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Cerebello-Striatal Connectivity and Implicit Learning in Autism Spectrum Disorders

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Dedication

To my friends, Harry Plumbley, Oscar Garcia, Jennifer Rittenhour, and my mother, Joan Morley, for spending long hours editing my work. To my brother David, for his providing me with advise on my analysis section. To my Father, Richard Morley, and my brothers, Tony and Daniel for standing beside me when I needed them.

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Cerebello-Striatal Connectivity and Implicit Learning in Autism Spectrum Disorders

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Previous studies have indicated that persons with autism spectrum disorder have distinct cerebella, striatum, and an impaired ability to anticipate implicit learning sequences; also, previous research indicates anatomic connections among these regions. Investigating distinctions in connectivity and impairments in the ability to anticipate implicit sequences linked to ASD would help clarify some of the core deficits associated with the disorder. This dissertation sought to explore differences in functional connectivity among the cerebellum, thalamus, and striatum. This dissertation would also seek to determine if an impaired ability to anticipate implicit sequences is associated with ASD. Twelve ASD participants and 11 control participants were scanned using an MRI while engaged in a modified serial reaction task. The findings indicate that the cerebellum and the striatum are functionally connected and the thalamus mediates this connection. The results indicate that ASD participants have stronger connections than the control, and ASD participants demonstrated some impairments in learning. However, there was not enough evidence to link ASD to an impaired ability to anticipate implicit sequences. This dissertation recommends that future studies consider the roles that these distinct connections play in symptoms of ASD.

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CHAPTER 1: INTRODUCTION

Statement of the Problem

Autism spectrum disorder is a heterogeneous group of disorders that impairs verbal and non-verbal social interactions (American Psychiatric Association, 1997). Moreover, autism can impair cognitive development in a variety of dimensions including thinking, memory, emotions, and attention (Delong, 1999). The Centers for Disease Control (2011) stated that autism impacts 1 in 110 children, which they contended is greater than pediatric cancer, diabetes, and AIDS combined (Gloeker-Ries, Percy Cl, Bunin GR 1999; National Center for Chronic Disease, 2001; National Center on Birth Defects & Developmental Disabilities, 1999). Additionally, the rate at which children have been identified as autism spectrum disorder [ASD] is increasing (Chakrabarti and Fombonne, 2005), and the rates at which children with ASD attend public school are also increasing (Dunlap, Kern, & Worcester, 2001). With climbing rates of autism, the demand for understanding the nature and nurture of the disorder accumulates. While current research has linked autism to a variety of sources, the etiologies are not known in the majority of cases (Schroeder, Desrocher, Bebko, & Cappadocia, 2010). Two potential areas of interest in autism relate developmental differences in neurological pathways and an impaired ability to learn implicitly. In this study, I seek to add to the understanding of how dysfunction in underlying neural networks might impact implicit learning deficits in ASD by investigating the link between functional connectivity, involving the cerebellum and the basal ganglia, and impairments in predicting implicit learning sequences.

Theories of Autism

Researchers have theorized models that provide explanations for the developmental differences characteristic of autism. Three contemporary theories that model developmental peculiarities of autism include the Weak Central Coherence Model, the Theory of Mind Model, and the Mirror Neuron Model.

Conceptualized by Frith and Happe, the Weak Coherence Model (WCM) describes autism as a cognitive bias towards local processing compared to global processing, which causes a propensity for persons with ASD to fail at understanding the context of given situations within the environment (Frith & Happe, 1994). This theory helps to explain persons' with ASD uneven profiles on IQ tests such as the Block Design Task, their preoccupation with parts compared to the whole, and repetitive/stereotypical behavior (Beaumont & Newcomer, 2006; Frith & Happe , 1994; Happe & Frith, 2006).

The Theory of Mind (ToM) Model suggests that the core deficit in autism relates to the inability to understand or interpret the mental states of others (Baron-Cohen, Leslie, & Frith, 1985). According to Baron-Cohen, Leslie, and Frith (1985), persons afflicted with ASD suffer from an impaired ToM. According to this theory, an impaired ToM engenders problems while engaging in social interactions. Baron-Cohen, Leslie, and Frith (1985) demonstrated support for this theory when they found that individuals with autism show inferior performance on false belief tasks compared with performances by typically developing peers. ToM is a key component of social cognition (Schroeder, Desrochera, Bebkoa, & Cappadocia, 2010). Social cognitive impairments are characteristic of autism.

A third contemporary theory concerning ASD pathology relates to mirror neurons (Schroeder, Desrochera, Bebkoa, & Cappadocia, 2010). Mirror neurons discharge when an observer witnesses another performing an action. This theory is based on findings contributed by Rizzolatti, Fadiga, Fogassi, and Gallese (1996), who found that cells within the premotor cortex were activated when actions were observed and/or when actions were performed. While this theory would seem to explain much in terms of problematic social interactions among ASD persons, evidence supporting this theory is minimal (Schroeder et al. 2010).

Each of these models may explain aspects of autism. None, however, can globally explain the heterogeneous assortment of ASD cases (Schroeder, et al. 2010). To complicate matters further, each model refers to different neurological correlates as supporting evidence. Relating to the weak central coherence theory, Iarocci and McDonald (2006) drew upon evidence of cerebellar abnormalities, which they contended enfeeble central coherence. Happe and Frith (2006) argued that weak central coherence relates to connectivity problems arising among the cortical and subcortical regions. Schultz (2005) implicated the orbitofrontal cortex, the medial prefrontal cortex, the inferior frontal gyrus, the superior temporal sulcus, the fusiform face area, the insula, brain stem, and the cerebellum as neurological correlates of social cognition. Finally, Oberman and Ramachandran (2007) suggested that the activation of motor neurons in the premotor cortex are functionally associated with the inferior frontal gyrus, the parietal lobe, the superior temporal sulcus, the striate cortex, the cerebellum, and the amygdala.

Although these models have different descriptions of ASD pathology and implicate different anatomical regions, they are not mutually exclusive (Schroeder, et al., 2010). More precisely, neurological differences in key areas could lead to widespread differences in other

areas of the brain. For example, all three models implicate cerebellar involvement. When taken in context of the cerebellum, abnormalities in the cerebellum may lead to abnormalities in cortical and subcortical regions, the insula, fusiform face area, and other regions (Allen, 2006).

Another potential area of convergence among these models relates to the processes underlying the models. Specifically, a process that underlies bias in processing, social cognition, and understanding the mental states and actions of others is implicit learning. Many researchers have suggested that the underlying source of impaired social interaction, communication, and motor deficits that describe autism and other pervasive developmental disorders relates to impairments in the ability to process and learn from unconsciously registered stimuli (Klinger et al., 2006; L. G. Klinger, Klinger, & Pohlig, 2007; Mostofsky, Goldberg, Landa, & Denckla, 2000; Romero-Munguıa, 2008). While research indicates that Autism Spectrum Disorder persons are able to learn implicitly (Barnes et al., 2008; Brown, Aczel, Kaufman, & Grant, 2010; Chun & Jiang, 1998; Nemeth, 2010), research indicates that autism impacts the ability to anticipate or adapt to implicit stimuli (De Cruz et al., 2009; Draher & Gaffman, 2002).

In reference to this intersection of neurological dysfunction and problematic impairments in the ability to predict implicit stimuli, research findings point to the cerebellum and the striatum. Notably, research has indicated pathologies within ASD cerebella (Allen, 2006; Courchesne & Allen,1997; Ornitz, 1983) and the ASD striatum (Qui, Adler, Crocetti, Miller, & Mostofsky, 2010; Sears et al., 1999; Weigel et al., 2010). Likewise, empirical studies suggest that the striatum and the cerebellum are involved in implicit learning (Doyon et al., 1996; Pascual-Leone et al., 1993). Considering that these two structures are connected anatomically (Hoshi et al., 2004) and functionally (Allen, 2005), it seemed promising to investigate the

functional connectivity involving the cerebellum and striatum and if differences in connectivity exist in a sample of ASD participants. Furthermore, it seemed promising to understand how this pathological connectivity impacts implicit learning among ASD persons.

The Purpose of this Study

This study addressed three goals: (1) to test a model of functional connectivity involving the cerebellum and striatum during an implicit learning task for healthy participants; (2) to test for differences in functional connectivity between Autism Spectrum Disorder participants and non-Autism Spectrum Disorder participants; and (3) to compare Autism Spectrum Disorder and non-Autism Spectrum Disorder participants' performance on an implicit learning task.

The first goal of this study involved testing a model of functional connectivity between the cerebellum/dentate and the striatum/putamen during an implicit learning task. While many studies have found anatomical connections between these regions, no study to date employs Sobel's mediation test to analyze connectivity between these regions during an implicit learning task.

The second goal involved comparing the functional connectivity model described in the first goal to determine if ASD participants demonstrate differences. Despite evidence supporting the differences within these implicated regions among ASD participants and supporting their involvement in implicit learning, research has yet to compare connectivity differences between Autism Spectrum Disorder and non-Autism Spectrum Disorder participants directly.

The third goal involved comparing differences in performance between Autism Spectrum Disorder and healthy participants on an implicit learning task. Several studies have compared the performance of ASD participants to healthy control groups. However, there has yet to be a study

that enlists an implicit learning task that presents the implicit sequence on using different sensory modalities.

Research Questions to be answered:

Research Question 1: Will participants display functional connectivity between each dentate nucleus and contralateral putamen?

*Research Question 2***:** Do participants with autism spectrum disorder display greater functional connectivity between the bilateral dentate and the bilateral putamen compared to the control group?

Research Question 3: Do participants with Autism Spectrum Disorder demonstrate learning impairments on the implicit learning task compared to the control group as indexed by reaction times?

In the following chapter, I discussed the research literature relevant to the intersection of autism, implicit learning, the cerebellum, the basal ganglia, and functional connectivity. In Chapter Three of this dissertation, I present my methods relevant to this study, the participants, the measures, my hypotheses, and the proposed analysis I used. In Chapter Four, I present my results , and in Chapter Five, I will discuss my findings.

CHAPTER TWO: REVIEW OF THE LITERATURE

This chapter will provide a review of the empirical literature relating to autism, the cerebellum, the basal ganglia, and implicit learning. In this review, I discuss the following: (1) the role of the cerebellum and basal ganglia in autism and implicit learning; (2) how differences in connectivity between the cerebellum and the basal ganglia may lead to impairments in autism.

Autism

Autism is a neurodevelopmental disorder that is associated with pervasive impairments (Scott, 2009). Specifically, autism is a spectrum or group of disorders that impairs verbal and non-verbal social interactions and also may impair cognitive development (American Psychiatric Association, 1997). Autism was first identified by Kanner (1943) as a cluster of symptoms in a sample of children (Smith, 2003). The symptoms that Kanner observed included a preference for social isolation, impairments in language, and a need for "sameness" (Smith, 2003). Autism was first recognized as a pervasive developmental disorder in 1980 (Smith, 2003). Since then, numerous empirical inquiries have attempted to understand the etiology and the pervasiveness of this disorder.

Research indicates that autism is a spectrum of heterogeneous disorders with symptoms varying in levels of functioning and severity (Amaral, Schumann, & Nordahl, 2008). Further, autism may have multiple causes and varying comorbid disorders (Amaral, Schumann, & Nordahl, 2008), leading some researchers to suggest that autism may result from multiple

genotypes (Amaral, Schumann, & Nordahl, 2008; Geschwind & Levitt, 2007). In addition, there is substantial heterogeneity in the onset of autism with most cases typically occurring before the age of three and some children demonstrating signs of delay within 18 months of life (Smith, 2003). Werner & Dawson (2005) estimated that 25 to 40 percent of children appear to develop normally followed by a sudden regression associated with symptoms characteristic of autism. It has been noted that some children show symptoms at birth (Smith, 2003).

Autism is characterized by symptoms in three primary domains that include language and communication, social interaction, and repetitive behaviors/restrictive interests (Scott, 2009). In terms of language specifically, children with Autism Spectrum Disorder suffer from impairments in language development (Lord & Paul, 1997; Tager-Flusberg, 1995). In fact, one of the early signs of autism includes a child's lack of responsiveness to his or her parent's voice (Smith, 2003). Impairments in language range from a lack of appropriate tonality, rate, and prosody (Tager-Flusberg, 1995) to the inability to develop any functional language (Lord & Paul, 1997). Even non-verbal communication, such as making appropriate facial expressions, is impaired or altogether absent (Smith, 2003; Wetherby & Prutting, 1984). Williams, Goldestein, and Minshew (2006) found that higher functioning individuals with autism demonstrated better language skills compared to lower functioning individuals with autism. However, both groups demonstrated impairments in complex language tasks.

Another deficiency characteristic of autism involves impairments in social interactions. Children identified as ASD tend to display deficits when interacting socially (Church, Alisanski, & Amanullah, 2000; Knott, Dunlop, & McKay, 2006; Kylliainen & Hietanen, 2004; Kylliainen & Hietanen, 2006; Macintosh & Dissanayake, 2006; Perphrey et al. 2002; Speer, Cook,

McMahon, & Clark, 2007; Weiss & Harris, 2001). Deficits include impairments involving initiating social interaction, interpreting verbal and non-verbal social cues, inappropriate emotional responses with others, and a lack of empathy (Weiss & Harris, 2001) as well as difficulty cooperating with others (Macintosh & Dissanayake, 2006). These problems often lead to difficulties in obtaining and maintaining friendships (Gutstein & Whitney, 2002) and frequently result in rejection and ridicule by peers (Church, Alisanski, & Amanullah, 2000). Furthermore, research indicates that high-functioning ASD children are often aware of these difficulties (Knott, Dunlop, and McKay, 2006; Rao, Beidel, & Murray, 2008). For instance, Knott, Dunlop, and McKay (2006) conducted a study comparing self-reported social skills and social competence for children and adolescents diagnosed with high-functioning autism and Asperger's syndrome to a control group. They found that children and adolescents with Asperger's and high-functioning autism reported a statistically significant deficit in social skills and social competence. Furthermore, research indicates that ASD persons tend to avoid looking at faces and making eye contact, and seem to feel uncomfortable when others gaze at them (Kylliainen & Hietanen, 2004; Kylliainen & Hietanen, 2006; Perphrey et al. 2002; Speer, Cook, McMahon, & Clark, 2007).

The third primary symptoms characteristic of autism involves ‘‘restricted, repetitive and stereotyped patterns of behavior, interests, and activities’’ (American Psychiatric Association, 1994). According to the DSM-IV (1994), this characteristic involves "abnormal focusing on a restricted pattern of interest, repetitive motor mannerisms, an inflexible adherence to nonfunctional routines or rituals, stereotyped and repetitive mannerisms, and a persistent preoccupation with parts of an object." This particular attribute of autism has not received the

same attention from researchers compared to impaired social interactions or communication (Lewis & Bodfish, 1998; Rutter, 1996). Despite receiving less attention, these behaviors and interests can be disruptive and socially inappropriate, often leading to social stigmatization (Gordan, 2000). Further, these behaviors can be detrimental to learning (Varni, Lovaas, Koegel, & Everett, 1979). The types of repetitive behaviors displayed by ASD persons vary from case to case (Cuccaro et al., 2003; Szatmari et al., 2006). These behaviors can range from tics to self-injury (Lewis & Bodfish, 1998) and the severity of these behaviors are positively correlated with the severity of autism (Prior & Macmillan, 1973) and negatively associated with IQ (Bartak & Rutter, 1976; Campbell et al., 1990).

The Cerebellum and Autism

Research has uncovered structural differences in several regions of the brain that may contribute to the symptoms of autism (Allen, 2006). One possible region of interest (ROI) is the cerebellum.

The cerebellum receives information from multiple regions of the brain including the prefrontal cortex, the temporal cortex, the amygdala, the hippocampus (Grossberg & Seidman, 2006), and the basal ganglia (Bostan, Dum, & Strick, 2010). Traditionally, the cerebellum has been theorized to be involved in motor coordination. However, research suggests that the cerebellum is involved in several other processes including attention, memory, learning, emotions, empathy, and language (Allen, 2006). Furthermore, research studies suggest that the cerebellum may be involved in autism as well as several other neurological disorders (Allen, 2006; Grossberg & Seidman, 2006; Hoppenbrouwers, Schutter, Fitzgerald, Chen, & Daskalaki,

2008).

Empirical studies reveal that the Autism Spectrum Disorder cerebella are different when compared to non-Autism Spectrum Disorder cerebella (Allen, 2006; Courtchesne & Allen 1997, Ornitz, 1983). Specifically, postmortem studies of individuals with autism reveal a reduction in the Purkinje cells of the cerebellum (Lee et al., 2002; Bailey et al., 1998; Fehlow, Bernstein, Tennstedt, & Walther, 1998; Kemper & Bauman, 1998; Ritvo, Freeman, Scheibel, Duong, & Robbinson, 1986; Vargas et al., 2005; Wegiel, 2004; Williams, Hauser, Purpura, Delong, & Swisher, 1980). More specifically, researchers have found a reduction in the number of Purkinje neurons in the cerebellum of individuals diagnosed with autism (Allen, 2006; Hoppenbrouwers, Schutter, Fitzgerald, Chen, & Daskalaki, 2008). Vargas et al. (2005) found a reduction in Purkinje neurons in nine out of 10 cases. Wegiel (2004) found that individuals diagnosed with autism had a 41 percent reduction in Purkinje neurons compared to a control group. Bailey et al. (1998) found a reduction in Purkinje neurons in five out of seven cases of autism, specifically in the vermis and the hemispheres of the cerebellum. Lee et al. (2002) found a similar reduction in the Purkinje neurons in the vermis and hemisphere of two cases.

In addition to postmortem studies, magnetic resonance imaging (MRI) has established evidence of a link between peculiarities in the cerebellum and ASD. Carper and Courchesne (2000) conducted a study consisting of 42 patients with autism and 29 participants in a control group without autism. They found that the patients with autism's vermis lobules VI-VII were significantly smaller than the control group. Moreover, they found an inverse correlation between cerebellum and frontal lobe size among the patients with autism but not the control group.

McAlonan et al. (2008) found results that support these findings. Specifically, they conducted Voxel-Based Computational Morphometry on a group of 33 children with Asperger's and high functioning autism (HFA) plus a control group of 55 children balanced for age, IQ, gender, maternal language, and ethnicity. They found that the Asperger's and HFA group had significantly less grey matter in their cerebellum compared to the control group.

Thus far, I have discussed previous research findings suggesting that individuals suffering from ASD have smaller cerebella compared to those persons not afflicted with autism. However, simply having smaller brain structures does not suggest a cause for autism. Rather, research should link cerebellum size to symptoms of autism.

The cerebellum has been linked to many cognitive functions that are impaired in autism including attention (Akshoomoff & Courchesne, 1992; Allen et al., 1997; Gottwald et al., 2003; Hodge, 2010; Lee et al., 1998; Riley, Homewood, &Walters 2011, Townsend et al., 1999), working memory (Desmond et al., 1997; Hodge, 2010), reasoning (Goel et al., 2000; Rao et al., 1997), and problem solving (Kim et al., 1994). Considering that research indicates that persons with ASD possess smaller cerebella and that cognitive functions associated with the cerebellum are distinct in autism, it is logical to suggest a link between the cerebellum and the symptoms of autism. Research supports this link between differences in the cerebellum and symptoms of autism (Allen, 2006; Allen et al., 1997; Courchesne, Townsend, and Saitoh, 1994; Muller et al., 1998;Townsend et al., 1999).

Additionally evidence has suggested a relationship between the cerebellum and pathology associated with autism such as IQ, impairments in communication, and repetitive behavior. For instance, Courchesne, Townsend, and Saitoh (1994) conducted a meta-analysis of multiple

studies, demonstrating a relationship between a reduction in the cerebellar vermis size and IQ. Two other symptoms characteristic of autism include an impaired ability to communicate and repetitive behavior. Previous research using positron emission tomography (PET) scans reveal an association between reduced cerebella activities for ASD participants while listening to sentences read aloud (Muller et al., 1998) and increased activity while listening to repetitive sentences compared to non-ASD participants (Muller et al., 1999). Muller et al. (1998) found a similar increased activation for ASD participants compared to a non-ASD control group while performing speech-related tasks. In summation, research suggests a cerebellar involvement and symptoms of autism.

The Role of Purkinjie Cells in Autism

As previously indicated, research suggests that autism may be related to an unusually small cerebellum. Further, postmortem studies have linked a distinctly small cerebellum to a reduction in cerebellar Purkinje cells. Finally, research indicates a link between differences in the cerebellum and symptoms of autism. Taking all this together, Allen (2006) proposed a model suggesting a link in the reduction of Purkinje cells to the symptoms of autism. The role of Purkinje cells in the cerebellum is to inhibit excitatory outputs from the deep cerebellar nuclei to other parts of the brain (Allen, 2006). As indicated by Figure 1, without the Purkinje cells to inhibit these nuclei, increased output leads to aberrant increases in activity of other parts of the brain. This activity would then lead to a strengthening of connections to other regions of the brain including the prefrontal cortex (Allen, 2006). These increased connections could decrease the overall brain efficiency and might contribute to the symptoms of autism (Allen, 2006).

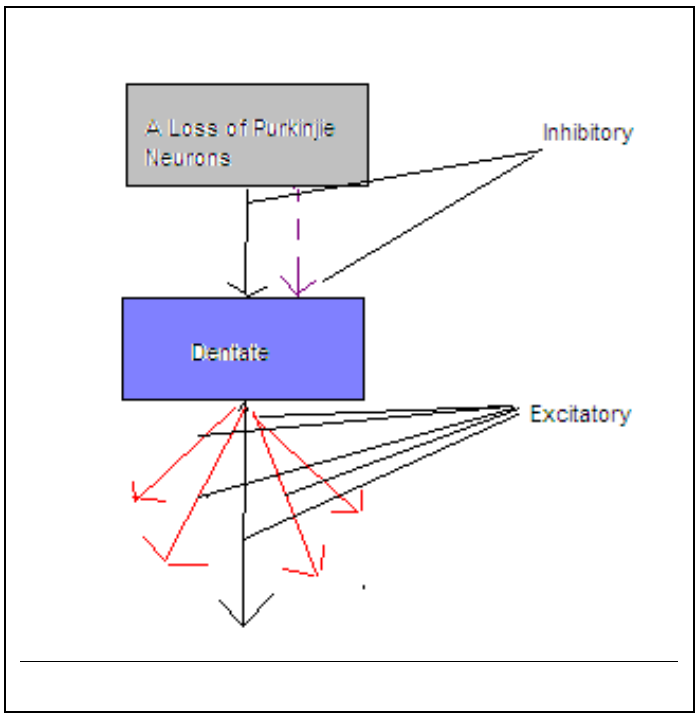


Figure 1: The loss of Purkinje cells increases the excitatory outputs of the dentate to other regions within the brain.

To summarize, previous research consists of empirical findings that indicate that Autism Spectrum Disorder persons tend to have smaller cerebella and that these differences in cerebellar size may be linked to certain symptoms of autism. While evidence corresponding to cerebellar peculiarities and autism is compelling, other regions, including the basal ganglia, also have been implicated in autism.

Basal Ganglia and Autism

The basal ganglia are a group of subcortical structures including the striatum, globus pallidus, subthalamic nucleus and the substantia nigra (Seger, 2006). The striatum, consisting of the caudate nucleus and the putamen, receives projections from several regions in the brain including the cerebellum (Hoshi et al., 2004, Allen, 2003; Allen, 2005), while the globus pallidus

is the primary output nucleus of the basal ganglia. The basal ganglia are interconnected with the cerebral cortex and several sub-cortical structures (Seger, 2006).

Researchers have compared the basal ganglia volumes of Autism Spectrum Disorder persons to non-Autism Spectrum Disorder controls with mixed results (Qui, Adler, Crocetti, Miller, & Mostofsky, 2010), some finding no differences in basal ganglia volumes (Sears et al., 1999; Hardan, Kilpartick, Keshavan & Minshew, 2003) and one finding that suggests differences in shape (Qui, Adler, Crocetti, Miller, & Mostofsky, 2010). Sears et al. (1999) compared the volumetric basal ganglia of 35 high-functioning ASD persons to 36 controls while matching for IQ, gender, and age. In terms of the overall volume of the basal ganglia, they found no difference between groups. Similarly, Hardan, Kilpatrick, Keshavan, and Minshew (2003) compared the basal ganglia of 41 high-functioning persons diagnosed with autism to 41 healthy controls. As with Sears et al (1999), they found no difference in overall basal ganglia size despite controlling for total cerebral volume. Qui et al. (2010) compared the basal ganglia of 32 ASD boys 8-12 years of age to a 45 participant age-matched control group. They did not find a significant difference in the overall size of the basal ganglia, though they did indicate differences in terms of shape. While researchers have not found a difference in proportional overall size of the basal ganglia, their findings indicate differences in the striatum among people diagnosed with autism (Hardan, Kilpartick, Keshavan & Minshew, 2003; Hollander, et al. 2005; McAlonan, et al. 2002; Qui, et al., 2010; Sears et al., 1999; Weigel et al., 2010).

While Spears et al. (1999) did not find a significant difference in the overall volume of the basal ganglia in ASD persons compared to the control groups, they did find a significant increase in the volume of the caudate. Hollander et al. (2005) compared the basal ganglia of 17

ASD participants to 17 controls and found that ASD participants had a significant increase in the right caudate and the overall volume of the putamen. Langen, Durston, Staal, Pamen, and Engeland (2007) looked at developmental trajectories of ASD caudate volume. They compared the striatum of 99 high functioning ASD participants to 88 participants in the control group. They found an interaction between age and caudate volume. Specifically, their results indicated that although normal developing children's caudate decreased with age, Autism Spectrum Disorder children's caudate increased with age, with the greatest increases in the right caudate.

In addition to unusual volume sizes, research suggests a link between the peculiarities in the caudate and symptoms of autism. Rojas et al. (2006) found a positive correlation between caudate size and repetitive behaviors. Hollander et al. (2005) found similar results; specifically they found a positive correlation between the size of the caudate and repetitive behavior. However, they found a negative correlation between caudate size and the ASD symptom relating to the ASD diagnostic interview of insistence on sameness repetitive behavior score on the Autism Diagonostic Interview-C domain. Spears et al. (1999) found a negative correlation among the caudate size, compulsions, and rituals and a positive correlation between caudate size and complex mannerisms. This suggests an interaction between caudate size and type of repetitive behavior. Despite these discrepancies, Langen et al. (2009) argued that these results are not contradictory. Specifically, they contended that complex mannerisms are a "lower order" repetitive behavior, and therefore are associated with increases in caudate volume. Furthermore, they suggested that "higher ordered" behaviors were negatively associated with caudate volume.

In addition to repetitive behavior, one study found evidence indicating that the striatum is involved in symptoms of autism involving social, communication, and motor dysfunctions (Qui,

et al., 2010). Qui, et al. (2010), found that among ASD participants, the size of the medial caudate predicted deficits in reciprocal, non-verbal social behaviors, and communications (as indicated on the ADOS-G) and the right posterior putamen predicted motor dysfunction.

In summary, this section links basal ganglia and empirical research suggesting a link between the basal ganglia and autism. Specifically, this research suggests that Autism Spectrum Disorder persons tend to have both a larger caudate and putamen compared to non-Autism Spectrum Disorder controls. Furthermore, research suggests that the caudate for ASD children increases with age while the caudate of normal children decreases with age. Further still, research indicates a link between some of the social and communication dysfunctions characteristic of autism and the size of the caudate. Additionally, the literature indicates a relationship between motor dysfunctions and the size of the putamen. Taken together, research indicates abnormalities in the cerebellum and in the basal ganglia occur in autism. An intersection between research involving the cerebellum, the basal ganglia, and autism is discussed in the next section.

Implicit Learning

Implicit learning involves the acquisition of information or a motor skill with minimal conscious awareness (Perrutchet & Pacton, 2008; Reber, 1967). Based upon a series of studies, implicit learning was conceptualized by Reber (1967). Reber (1989) contended that implicit learning involves anticipating changes without any reportable awareness, although this view is not without its detractors (Perruchet, 2008; Shanks, Rowland, & Ranger, 2005). Many researchers argue that implicit learning is a process involving an increase in responsiveness to

environmental stimuli without intention to learn and the inability to articulate the learning that occurred (Berry & Dienes, 1993; Cleeremans & Dienes, 2008; Gluck, Shohamy, & Myers, 2002; Perruchet, 2008; Shanks, 2005). The ongoing debate over implicit learning covers two decades among researchers attempting to understand how consciousness plays a role in cognition (Cleeremans & Dienes, 2008).

Although highly related to implicit memory, implicit learning is conceptually different. Specifically, implicit learning relates to acquiring and generalizing a change in response to new stimuli (Cleeremans & Dienes, 2008). Implicit memory involves the retention of this change in stimuli acquired through whatever form of implicit learning (Cleeremans & Dienes, 2008).

Implicit learning is often contrasted with explicit learning, that is, learning for which the learner can fully express awareness of the knowledge or concept learned (Berry & Dienes, 1993; Cleeremans & Dienes, 2008; Shanks & St John, 1994; Shanks, Wilkinson, & Channon, 2003). While research attempting to distinguish between these two types of learning has proven problematic, it has demonstrated some distinctions (Shanks & St. John, 1994; Shanks, Wilkinson, & Channon, 2003). Specifically, implicit or procedural learning has been differentiated from explicit or declarative learning in terms of behavior and neurological systems (Squire, 1994). One way in which implicit learning has been differentiated from explicit learning relates to dependency on IQ. Several researchers indicated that while explicit learning is correlated with IQ, implicit learning has been found to be independent of IQ (Brown, Aczel, Jimenez, Kaufman, & Grant, 2010; Kaufman et al., 2009; Gebauer & Mackintosh, 2007; Reber, Walkenfeld, & Hernstadt, 1991). Another difference relates to the ability of amnesiacs to improve performance on implicit learning tasks (Knowlton, Squire, & Gluck, 1994). Patients

suffering from anterograde amnesia show an impaired or complete lack of explicit learning. Knowlton, Squire, and Gluck (1994) demonstrated decreases in reaction time on the implicit learning tasks for some amnesiac patients.

Another distinction between implicit and explicit learning involves attention. Specifically, evidence suggests that implicit learning requires less attention than explicit learning (Destrebecqz & Cleeremans, 2001; Willingham, 2001; Willingham & Goedert-Eschmann, 1999; Seger, 1994; Shanks & John, 1994; Squire, 1992; Reber, 1989). While researchers generally agree that explicit learning is dependent on attention (Cleeremans & Jime´nez, 1998), they disagree on how much implicit learning is dependent upon attention (Shanks, Rowland, & Ranger, 2005; Nissen & Bullemer (1987)). In order to provide a distraction to test the effects of attention on implicit learning, Nissen and Bullemer (1987) added a tone-counting task to the serial reaction task. They found a lack of implicit learning under the dual-task condition. However, Statler (1995) contended that the tone-counting task did not reduce attention per se; rather, it interfered with the sequence of the serial-reaction task. Shanks, Rowland, and Ranger (2005) added a second task to the experimental group to test the attentional demands of the second task on implicit learning. They found that the secondary task did affect performance on the implicit learning task.

Despite these differences, implicit and explicit learning systems seem to be related (Libet, Gleason, Wright, & Pearl, 1983; Libet, 1985; Squire & Zola, 1996; Willingham & Goedert-Eschmann, 1999). For instance, in the Knowlton, Squire, and Gluck (1994) study, the control group demonstrated greater performance once the task was extended over 50 trials. Also, research has indicated that implicit learning generally precedes explicit learning (Fischer,

Drosopoulos, Tsen, & Born, 2006**;** Libet, 1985; Libet, Gleason, Wright, & Pearl, 1983; Mathews, Buss, Chin & Stanley, 1988; Reder, 1987). Fischer, et al. (2006) examined the effects of sleep on implicit and explicit learning. They implemented an implicit learning serial-reaction task to test implicit learning in a sleep group and a sleep deprived control group. During the first test, neither group demonstrated any explicit knowledge of the task's implicit sequence. After the sleep group slept for a nine-hour interval, the researchers tested both groups. They found that the sleep group demonstrated explicit learning of the sequence while the sleep deprived control group did not display any explicit learning improvements. Libet, Gleason, Wright, and Pearl (1983) conducted a study that provided evidence that implicit learning precedes explicit learning. Concisely, participants were connected to an EEG and asked to record the position of a dot on an oscilloscope timer while performing a motor task. Researchers then recorded the time the subjects noticed the dot to the time that they marked the dot by pushing a button. They found the subjects pressed the button prior to explicitly realizing the dot location, thus concluding that implicit perception preceded explicit perception.

In terms of measuring implicit learning, researchers have employed multiple methods (Cleeremans & Dienes, 2008), including the Serial Reaction Time (SRT) task, the Contextual Cueing (CC) task, the Probabilistic Category Learning (PCL) task, and the Artificial Grammer Learning (AGL) task. With each of these tasks, implicit learning is measured by the discrepancy between participants' performance on a task and their ability to describe verbally a change in performance on this task (Cleeremans & Dienes, 2008). The AGL task (Reber, 1967) involves measuring the difference between the subjects' ability to classify the rules of grammar on memorized, meaningless letter strings and their ability to verbally describe the rules of grammar

that apply to these strings. As indicated by Reber, participants appear "sensitized" to these rules of grammar yet are unable to describe them. The PCL task (Gluck & Bower, 1988) measures the participants' ability to classify stimuli without explicit knowledge of the relationship between the stimuli and the outcome. The CC task (Chun & Jiang, 1998) involves participants visually searching a display of stimuli with half of the stimuli following a predictable sequential pattern of distracter stimuli. This task measures implicit learning by calculating the participants' increases of performance on the predictive sequential tasks. Similar to the CC task, the SRT task (Clegg, DiGirolamo, & Keele, 1998) involves measuring participants' decreases in reaction time on a predictive sequential task versus a random sequence task. The serial reaction has been the dominant measure of implicit learning in the research literature (Cleeremans & Dienes, 2007; Segeir, 2006).

In summary, implicit learning is conceptually separate from explicit learning in that it falls outside the domain of declarative memory. Implicit learning seems to place less demands on attention than explicit memory, precedes explicit learning, and often runs concurrent with explicit learning. In addition, this section describes the current measures of implicit learning. In the next section, I will review research examining neurological systems and how they relate to implicit learning.

Implicit Learning and the Brain

The relationship between implicit learning and regions of the brain has captured the interest of many researchers (Vries, Ulte, Zwisterlood, Szymanski, &Knecht, 2010).

While the regions of the brain implicated in explicit and implicit learning are parallel (Aizenstein

et al., 2004; Destrebecqz et al. 2003; Hazeltine & Ivry 2003; Dennisa & Cabezaa, 2010) and often complimentary (McDonald & White, 1993; Mitchell & Hall, 1988; Packard et al., 1989), research suggests that the systems involved in each are independent (Jenkins et al., 1994; Poldrack and Gabrieli, 2001; Poldrack et al., 2001). Current research suggests multiple regions are involved in implicit learning, including the basal ganglia and the cerebellum (Shohamy, Myers, Kalanithi, & Gluck, 2008; Naismith et al. 2010; Ullman, 2004*)*. In contrast to explicit learning, which seems primarily to involve the medial temporal lobe (Cohen et al., 1985; Cohen et al., 1999), research suggests that the cerebellum, striatum, and motor cortices (Fletcher et al., 2005; Rauch et al., 1997; Wilingham, Salidis, & Gabrieli, 2002) as well as the prefrontal regions (Shohamy, Myers, Kalanithi, & Gluck, 2008; Ullman, 2004) are involved in implicit learning tasks. One region that has captured a substantial amount of interest is the basal ganglia (Heindel et al., 1989; Knowlton et al., 1996; Knowlton, 2002; Shohamy, Myers, Kalanithi, & Gluck, 2008; Ullman, 2004).

Basal Ganglia and Implicit Learning

Currently, the consensus among researchers drawing data from neuroimaging, animal, Parkinson disease, Huntington disease, and lesion studies suggests that the basal ganglia is directly involved in implicit learning (Heindel et al., 1989; Knopman & Nissen, 1991; Willingham & Koroshetz, 1993; Knowlton et al., 1996; Knowlton, 2002; Muslimovic, Post, Speelman, & Schmand, 2007; Shohamy, Myers, Kalanithi, & Gluck, 2008; Ullman, 2004). Unlike patients with frontal lobe lesions (Knowlton et al., 1996) and medial temporal lesions (Eldridge, Masterman, & Knowlton, 2002; Knowlton, Mangels, et al., 1996; Knowlton et al.,

1994), patients with lesions or degenerations of the basal ganglia perform poorly on implicit learning tasks (Kéri et al., 2002; Knowlton et al., 1996; Knowlton, Squire, Paulsen, Swerdlow, & Swenson, 1996; Mayor-Duboisa, Maederb, Zesigerc, & Roulet-Pereza, 2009). Kéri et al. (2002) conducted a case study of a patient afflicted with cerebral angiitis, which caused predominant damage to the right neostriatum, and compared the patient to three control patients afflicted with parietal lobe damage. Both the experimental group and the control group demonstrated impairments on IQ, verbal memory, episodic memory, semantic memory, object recognition, attentional set shifting, and the probabilistic classification-learning task. After one month of steroid therapy, both groups demonstrated improvements on every test with the exception of the procedural learning tasks. While the three control patients demonstrated significant improvement on the procedural learning tasks, the patient with right striatum damage remained impaired. The researchers hence suggested a distinct difference between the striatal-mechanism for procedural learning and attention. Another study by Mayor-Duboisa, Maederb, Zesigerc, and Roulet-Pereza (2009) compared 18 children with basal ganglia lesions and other various basal ganglia dysfunctions to a control group of 72 age-equivalent participants on the serial reaction task and the probabilistic category-learning task. While the control group demonstrated a significant increase in implicit learning on each task, the children with basal ganglia dysfunctions did not show a significant decrease in reaction time on either task.

Research on basal ganglia dysfunction and its impact on implicit learning is dominated by studies on degenerative diseases such as Parkinson's and Huntington's (Saint-Cyr et al., 1995). Similar to the findings in lesions studies, a link has been noted by several researchers between degenerative basal ganglia disorders and impairments in implicit learning (Doyon et al.,

1997; Knopman & Nissen, 1991; Jackson, Jackson, Harrison, Henderson, & Kennard, 1995; Muslimovic, Post, Speelman, & Schmand, 2007; Pascual-Leone et al., 1993; Stefanova, Kostic, Ziropadja, Markovic, & Ocic, 2000; Willingham & Koroshetz, 1993). Parkinson's disease is a degenerative neurological disorder characterized by the degeneration of the nigrostriatal systems. Several studies have concluded that patients diagnosed with Parkinson's demonstrate an impaired performance on implicit learning tasks when compared to healthy controls (Frith et al., 1986; Haaland et al., 1997; Harrington & Haaland, 1999; Heindel et al., 1989; Jackson et al., 1995; Westwater et al., 1998), patients with amnesia resulting from medial temporal lobe damage, and those with frontal lesions (Knowlton, Mangels, & Squire, 1996). Knowlton, Mangels, and Squire (1996) contrasted 20 patients diagnosed with Parkinson's disease to 12 patients with retrograde amnesia (due to hippocampus damage) and 10 patients with prefrontal lesions on a probability-classification task. Results indicated that persons diagnosed with Parkinson's demonstrated a significantly decreased ability on performance compared to patients with amnesia. Further, Parkinson's patients performed significantly lower than patients with prefrontal lesions. However, this significance was weak ($p < 0.10$); it can be argued that this could be due to a small sample size. Jackson et al. (1995) found similar results when comparing 11 participants diagnosed with Parkinson's disease to 10 age-matched controls on the serial reaction task. Specifically, the participants with Parkinson's demonstrated a higher reaction time compared to the control on the implicit learning sequence of the serial reaction tasks.

Researchers have found similar results with persons with Huntington's disease (Knopman & Nissen, 1991; Knowlton et al. 2006; Willingham & Koroshetz, 1993). Huntington's disease is caused by a degeneration of the caudate and the putamen. Knopman and Nissen (1991)

compared 13 patients diagnosed with mild to moderate Huntington's disease to a 10-person, age-matched control group on the serial reaction task. Not only did Huntington's patients demonstrate an impaired reaction time on the serial reaction task compared to the control, but five patients failed to show any significant learning on the sequence-learning section of the task. Knowlton et al. (1996) found similar results when comparing 13 Huntington's patients to a 12-participant control group on motor probabilistic-categorical learning tasks. Knowlton et al. also found similar results on 10 Huntington's patients compared to a control group consisting of 12 participants on a non-motor, probabilistic-learning task. Independent of motor function, the Huntington's patients demonstrated significant impairments compared to the control groups on probabilistic learning.

In addition to lesion and basal ganglia degeneration studies, functional imaging studies have demonstrated a relationship between the basal ganglia and implicit learning (Grafton, Hazeltine, & Ivry, 1995; Rauch et al., 1997). Rauch et al. (1997) used fMRI to study brain activation for 10 right-handed participants performing a serial reaction task. They found significantly increased activations in the right caudate, left caudate, and the putamen during the learning phase compared to the random control group. Similarly, Kim et al. (2004) compared the fMRI activation of eight mildly affected Huntington's patients to 12 healthy controls ' performance on a serial reaction task. The healthy control group demonstrated significant activations in the caudate and the putamen, while the Huntington's group showed activation only in the caudate. Further, only the control group demonstrated any decreases in reaction time on the serial reaction task.

To summarize, research indicates that the basal ganglia are directly involved in implicit

learning. More specifically, research indicates that persons who have suffered lesions or those with neurodegenerative disorders are impaired on implicit learning tasks. Further, neuroimaging research suggests a relationship between the caudate and the putamen and their relationship to the performance on implicit learning tasks.

Cerebellum and Implicit Learning

While the cerebellum has typically been associated with motor systems (Carlson, 2007), neuroimaging studies and lesion research indicate that the cerebellum plays a role in implicit sequence learning (Doyon et al., 1998; Pascual-Leone et al., 1993; Molinari et al., 1997). Further, research indicates that the cerebellum's role in implicit learning involves the ability to predict changes in the sequences of events (Bastian, 2006; Molinari et al., 1997; Ivry, 2000).

The majority of research supporting this link has been drawn from individuals suffering from cerebellar damage (Bastian, 2006), which indicates that participants with cerebellar lesions or dysfunctions demonstrate an impaired performance on implicit learning tasks (Pascual-Leone et al., 1993; Molinari et al., 1997; Doyon et al., 1998; Gomez-Beldarrain et al., 1998). Pascual-Leone et al. (1993) conducted a study comparing serial-reaction time of 20 Parkinson's disease patients, 15 patients with cerebellar degeneration, and 30 age-matched, healthy volunteers. Neither the patients with cerebellar degeneration nor those with Parkinson's disease demonstrated improvements on reaction time during the implicit-learning sequence of the serial-reaction task. Eventually, patients with Parkinson's disease achieved declarative knowledge of the procedure and used it to improve performance whereas patients with cerebellar degeneration failed to achieve declarative knowledge. Pascual-Leon et al. (1993) concluded that although the

basal ganglia and the cerebellum are involved in implicit learning, they have different functions. Specifically, they stated that the cerebellum may "index and order events." Molinari et al. (1997) found similar results comparing eight patients with cerebellar lesions to six healthy participants in the control group on a serial-reaction task in a series of four studies. In each study, the patients with cerebellar lesions displayed impairments on implicit sequence-reaction time even when controlling for motor response time, but not on the random sequence. Further, patients with cerebellar lesions display impairments in explicitly detecting a sequence over several runs. Further still, when the sequence was explicitly learned before testing, results were similar to the patients with cerebellar lesions, and significant improvements occurred in their reaction time. The authors concluded that the cerebellum is involved with "detecting and recognizing event sequences." (pg 1753)

In addition to lesion studies, neuroimaging data support a relationship between the cerebellum and implicit learning (Doyon et al. 1996; Pascual-Leone et al., 1993). Doyon et al. (1996) investigated the relationship between patterns of regional cerebral blood flow (CBF) and their relationship to implicit and explicit learning. Fourteen participants were scanned using positron emissions topography and functional MRI while engaging in an implicit serial-reaction task. Prior to the implicit learning task, one group was explicitly taught the sequence. While conducting the newly implicit task, researchers found a significant increase in activation of the dentate nucleus and the striatum compared to random controls. Further, they found more activation for the dentate and the striatum when the implicit sequence was novel or minimally practiced. While conducting the explicit task, however, they found significant activation only in the right ventrolateral frontal area. These researchers concluded that the cerebellum and the

striatum are involved in implicit learning.

One weakness in studies concerning the cerebellum and implicit learning relates to the cerebellum's role in motor performance (Seidler et al., 2002). Does the cerebellum mediate the relationship between implicit learning and improved motor performance or does implicit learning mediate the relationship between the cerebellum and the improved motor performance? Seidler et al. (2002) included a concurrent distracter task, which was used to suppress learning, followed by a sequence task without the distracter task. A functional MRI was conducted on six participants while they participated in each task. While no significant cerebellar activation or increases in performance were noted during the sequenced distracter phase, results indicated an increased cerebellar activation and increased performance occurring during the normal implicit learning phase. The researchers concluded that the cerebellum is not involved in the implicit acquisition of motor learning; rather, the cerebellum coordinates its expression.

Based on empirical findings such as these, many researchers contend that the cerebellum is involved in predicting changes in sequences (Bastian, 2006; Molinari et al., 1997; Ivry, 2000). Bastian (2006) contended that studies describing the effects of cerebellar damage on implicit learning demonstrate impairments in prediction rather than "reactive control" of sequenced learning. She based this on several findings that suggest that while motor ability is intact in persons with cerebellar damage (the ability to adapt to new circumstances), they seem to be impaired. Further, she stated that empirical findings suggest that specific predictions computed by the cerebellum relate to future sensory states. Restuccia, Giacomo, Leggio, and Molinari (2007) found support for this hypothesis using a mis-match negativity (MMN). The MMN is a component of an event-related response (ERP) that entails an odd sequence presented in a

sequence of stimuli. ERPs are electrophysiological responses to stimuli. Specifically, the researchers compared eight healthy volunteers to six patients with cerebellar lesions. They applied electrical stimulation to each participant, including an "odd ball stimulus," which includes frequent stimuli with rare, deviant, electrical stimulations to the thumb and fifth fingers on the left hand using labeled and modified frequent stimulation. This was labeled as a "stimulus ignored condition," where the subjects received regular electrical stimuli only to the fifth finger. In healthy participants, the "odd ball" sequence produced an event-related potential, while the patients with cerebellar degeneration demonstrated a lack of an event-related potential. The authors concluded that event-related potential elicited from the MMN demonstrates a predicted change. The lack of an event-related potential or the distinct event-related potential among participants with cerebellar lesions suggests that the cerebellum is involved in the prediction process of future stimuli.

In summary, research indicated that in addition to the basal ganglia, the cerebellum plays a role in implicit learning. Further research suggests that the specific role of the cerebellum in implicit learning involves detecting implicit stimuli and/ or predicting future implicit stimuli.

Autism and Implicit Learning

Many researchers have suggested that implicit learning contributes to the development of social, communicative, and motor skills (Kaufman et al., 2009; Meltzoff, Kuhl, Movellan, & Sejnowski, 2009; Perruchet, 2008). Since deficits in these three areas are characteristic of autism, some researchers have hypothesized that an impairment in the implicit learning process may be responsible for social, communication, and motor deficits characteristics of autism

(Klinger et al., 2006; L. G. Klinger, Klinger, & Pohlig, 2007; Mostofsky, Goldberg, Landa, & Denckla, 2000; Romero-Munguıa, 2008). Empirical evidence has varied, with some studies suggesting that implicit learning is impaired (Gordon & Stark, 2007; L. G. Klinger et al., 2007; Mostofsky et al., 2000). Some studies suggest that implicit learning processes are not impaired (Barnes et al., 2008; Brown, Aczel, Kaufman, & Grant, 2010; Chun & Jiang, 1998; Nemeth 2010). One study about implicit learning had mixed results, including inferior implicit learning when the stimulus is social (Smith, 2003).

Mostofsky et al. (2000) contended that autism spectrum disorder pathophysiology involves an abnormal cerebellum and that the cerebellar lesions have been linked to impairments in implicit learning. Consequently, persons diagnosed with autism are likely to demonstrate impaired performance on similar tasks. To test this hypothesis, Mostofsky compared the performance of participants with autism to 17 age-and IQ-matched controls on the serial-reaction task. Results indicated that autism spectrum disorder persons demonstrated significant impairments in terms of implicit learning. Neither group differed in terms of acquiring explicit knowledge of the task. In contrast, Gordon and Stark (2007) found evidence that, while impaired on implicit learning tasks, low functioning participants with ASD are capable of implicit learning if they receive prior exposure to the sequence. Specifically, they compared seven low functioning persons diagnosed with ASD to five age-matched boys serving as a control group. They found that although persons with ASD demonstrated significantly higher reaction time compared to the control group, their performance did significantly improve over time. Klinger et al. (2006) conducted a study comparing children with ASD to typically developed children who were matched for mental age using Peabody Picture Vocabulary Test (PPVT) on an AGL

implicit learning test with animals rather than letters. While L.G. Klinger found that participants with ASD demonstrated impairments on implicit learning, other researchers criticized this study on the basis that Klinger did not demonstrate between-group equivalence on I.Q. and chronological age (Brown et al., 2010). Barnes et al. (2008) found marginal ($p = 0.06$) serial-reaction differences between 14 higher functioning participants with autism spectrum disorder and 14 participants in a control group on a serial-reaction task. Further, Barnes et al. found an interaction in terms of sequential learning time between the ASD participants and the controls over five runs. More specifically, their findings suggested that ASD persons learned slower but more consistently over time. The author suggested that ASD persons' "expression of learning" lasted longer than the controls.

Brown et al. (2010) compared 31 children with ASD to 31 typically developing children while performing multiple implicit learning tasks, including the serial reaction task, contextual cueing, artificial grammar learning, and probabilistic-classification learning tasks. The authors claimed that both groups demonstrated equivalent learning on both tasks. Further, the authors contended that autism implicit-learning systems are enacted. However, they reported that persons with autism demonstrated slower performance in terms of reaction time on the contextual cueing and on the serial reaction tasks compared to the control group during the first block. Further, the difference between groups gradually became smaller as the task progressed.

To summarize, many researchers have theorized that persons with ASD suffer from an impaired ability to learn implicitly. Empirical evidence suggests that individuals diagnosed with autism retain the ability to learn implicitly. However, research suggests that ASD persons tend to demonstrate less implicit learning when initially engaging in a new sequence, gradually

improving until eventually they demonstrate similar performance with non-ASD persons.

Functional MRI

Functional MRI as a Measure of Neuronal Activity

Functional MRI (fMRI) involves the use of strong magnetic fields to create images of regions within the brain that are then linked to mental processes (Huettel, Song, and McCarthy, 2009). More specifically, fMRI measures changes in blood oxygenation over time that are associated with experimental tasks (Huettel, Song, McCarthy, 2009). This indirect measure of neuronal activity makes use of changes in hemodynamic response (HDR). HDR relates to decreases in the relative amount of paramagnetic hemoglobin characteristic of deoxygenated blood. This contrast in blood oxygenation level is measured through the Blood-Oxygenation-Level-Dependent contrast or BOLD (Huettel, Song, McCarthy, 2009). HDR fluctuations reflect changes in demands for oxygen, cereberal blood volume, or the flow of blood changes (Logothetis & Wandell, 2004; Ogawa, Lee, Nayak, & Glynn, 1990). Furthermore, these changes are considered inputs to cellular metabolism (Logothetis & Wandell, 2004). Since oxygen is a source of energy implemented by neurons during neuronal activity, this indicates that blood deoxygenation is a function of neuronal activity, thus the BOLD signal indirectly measures neuronal activity.

The Time Invariant Linear Convolution Model

One method of measuring the HDR involves modeling the BOLD signal as a convolution of a Hemodynamic Response Function (HRF) with a stimulus function (Henson & Friston, 2008).

(HR or Y) = (The time invariant Parameter or Beta) (The Time-series Data represented by X) + £(Error)

(Based off Henson & Friston, 2008)

More specifically, this model assumes that time associated with the experimental condition is a linear predictor of the BOLD signal (Monti, 2011). Further, the null hypothesis in this model assumes that the amplitude of hemodynamic peaks representing the BOLD signal decreases to zero over the time course in response to the experimental manipulation. A hemodynamic activation represents significant changes in slope over the time course. Typical activation models tend to target a subject's hemodynamic response provoked by an experimental manipulation (Nichols & Hayasaka, 2003). Since this model corresponds to single-subject data, multiple comparisons are often required. Due to the corrections required to account for type I error inflation, analysis of these models tends to be conservative (Nichols & Hayasaka, 2003).

The assumption of a linear relationship between time and HDR has found mixed support (Buxton et al., 1998; Cohen, 1997; Logothetis, 2003; Monti, 2011; Robson et al., 1998). Research seems to indicate that when stimuli are less than four seconds in length, they tend to violate the linearity assumption (Robson et al.,1998, Vasquez & Noll, 1998), even when violated results do not display an excessive impact on amplitudes (Miezin et al., 2000).

Functional Connectivity MRI

Functional imaging techniques that measure cerebral blood flow such as PET and fMRI

have become established methods for investigating the brain in living subjects (Postuma & Dagher, 2006). Advances in the functional MRI have led to empirical techniques for establishing relationships between brain regions (Huttel, Song, & McCarth, 2009). This technique, referred to as functional connectivity MRI or fcMRI, can be described as a correlation among regional hemodynamic response changes (Postuma & Dagher, 2006).

Friston (2009) defined connectivity in terms of statistical correlations "among remote neurophysiological events" (Filipi, 2009). FcMRI allows researchers to measure changes in activation throughout the entire brain, often while the participants are engaging in an experimental task (Huttel, Song, & McCarth, 2009). By establishing relationships among the hemodynamic responses of various regions of the brain during an experimental task, research can infer that these neurological systems are components of the functional system associated with the task (Huttel, Song, & McCarthy, 2009). Using FcMRI, researchers have mapped connections involving a wide variety of brain systems, including systems that relate to sensory, motor, and cognition functions (Biswal et al. 1995; Greicius et al. 2003; De Luca et al. 2006; Zhang et al. 2008).

FcMRI can establish functional connections, which are not necessarily the same as anatomic connections (Buckner et al. 2009*;* Postuma & Dagher, 2006). Functional connectivity implies that these regions are correlated while performing a specific task, while anatomic or monosynaptic connections involve direct synaptic connections (Huttel, Song,& McCarth, 2009). This is useful to researchers since monosynaptic connections are not necessarily involved in the specific task related function (Monchi et al 2004; Postuma & Dagher, 2006; Toni et al. 2002).

While inferring directionality for these connections is preferred and considering many

regions within the brain are bidirectional, FcMRI offers limited use on unearthing the directionality of these connections (Huttel, Song,& McCarth, 2009; Krienen & Buckner, 2009). Further, FcMRI can lead to ambiguous findings (Krienen & Buckner 2009). Specifically, it may be difficult to determine if one or more of these interconnected regions are mediators to other coactivated regions (Krienen & Buckner 2009). Due to the inherent difficulties in determining directionality, FcMRI has limitations inferring causality (Huttel, Song,& McCarth, 2009). Specifically, if it is difficult to determine the direction of the connection, it is likewise difficult to infer that one region activated the other region. However and despite these limitations, the FcMRI has been established as a powerful method for uncovering interconnected regions and the relationship that these regions have with behavior (Huttel, Song,& McCarth, 2009).

Unlike activation models, FcMRI analyzes correlations independent of stimuli. However, FcMRI has been combined with behavioral data through identifying correlations among psychophysiological interactions (Huttel, Song,& McCarth, 2009; Rissman, Gazzaley, & Desposito, & 2004). Psychophysiological fMRI research was originally developed by Friston et al. (1997) for the purpose of exposing subjects to a stimulus or having them engage in a behavior while observing how these stimuli or the behavior invoke regional activation within the brain (Huttel, Song,& McCarth, 2009). Rissman, Gazzaley, and Desposito (2004) combined FcMRI and psychophysiological fMRI by extracting activation coefficients from single subjects and employed correlations to compare the activation coefficients among multiple regions of interests (ROIs).

In summary, this section states that FcMRI is an established method of investigating functional connections between several regions within the brain, even if they are not

monosynaptic connections. Further, functional connectivity is established when two or more areas in the brain coactivate while engaging in a function or behavior. Further still, FcMRI possesses limitations in terms of determining direction of these connections or establishing causality. Finally, FcMRI has been used to examine the associations between behavior data and functional connections within the brain.

Connectivity between the Cerebellum and the Basal Ganglia

Early views concerning the connectivity between cerebellum and the basal ganglia were that the basal ganglia and the cerebellum are separated into distinct unconnected systems (Middleton & Strick, 2000). Current research supports a functional connection and an anatomical connection between the basal ganglia and the cerebellum (Allen et al., 2003*;* Allen et al., 2005; Bostan, Dum, & Strick, 2010; Doyon et al., 1996; Hoshi et al., 2005; Perciavalle et al., 1987).

Although researchers as early as Perciavalle et al. (1987) suggested an anatomical link between the cerebellum and the basal ganglia in a case study of a cat, most researchers did not appreciate the link until Hoshi et al. (2004) provided evidence of a direct link between these two sub-cortical structures within the brains of Macaques monkeys. More specifically, Hoshi et al. (2004) injected a strain of herpes, which involves a retrograde transport along neural paths, into the putamen and the globus pallidus. They found after injection into the putamen, the herpes was transported to the ventrolateral and the intralaminar thalamus and then to the dentate. After injection into the globus pallidus, the herpes was transported to the putamen and then to the ventrolateral/ intralaminar thalamus and then to the dentate. This suggests that the dentate projects to a main input structure of the basal ganglia, the putamen. Further, these results suggest that this link is mediated by the thalamus.

While results from Hoshi et al. (2004) provided evidence for disynatic projection from the cerebellum to the putamen in Macaques monkeys, Allen et al. (2005) applied a functional connectivity MRI to 12 healthy participants to investigate functional connectivity for the cerebellum and other regions of the brain, including the basal ganglia. After isolating the BOLD signal from the dentate, Allen et al. found functional coherence between the left dentate and the thalamus, bilateral caudate, and right putamen. According to their findings, the right dentate was functionally connected to the striatum, putamen, and the caudate in addition to the globus pallidus.

While evidence suggests that the cerebellum and the basal ganglia are connected and that the cerebellum projects through the thalamus to the putamen (Allen et al. 2005; Hoshi et al. 2004), a more recent study suggests that the basal ganglia projects to the cerebellum independently of the prefrontal cortex (Bostan, Dum, & Strick, 2010). Specifically, Bostan, Dum, and Strick (2010) injected the herpes virus into the cerebellum of Macaques monkeys. The retrograde transportation demonstrated multiple diasynaptic connections between the subthalamic nucleus mediated by the pontine nuclei and the inferior olive. This suggests that the basal ganglia projects to the cerebellum through the pontine nuclei and the inferior olive.

Based on these findings, research indicates a two-way communication between the cerebellum and the basal ganglia. More specifically, the dentate projects to the striatum through the thalamus, and the subthalmic nuclei project ultimately to the cerebellum.

The Role the Cerebellum and Basal Ganglia Play in Anticipating Implicit Sequences

As previously discussed, researchers have unearthed differences in the cerebellum (Allen,

2006; Courtchesne & Allen, 1997) and the basal ganglia among persons diagnosed with autism spectrum disorder (Qui, Adler, Crocetti, Miller, & Mostofsky, 2010). Further, researchers have uncovered an anatomical link between the basal ganglia and the cerebellum (Allen et al. 2003*;* Allen et al. 2005; Bostan, Dum, & Strick, 2010; Hoshi et al. 2005; Perciavalle et al., 1987). In addition to these findings, research suggested that the cerebellum and basal ganglia are involved in the ability to anticipate or predict change (Draher & Graftmen, 2002). In terms of autism, researchers have contended that these distinct connections may result in the impaired ability to anticipate or predict (Allen, 2006; De Cruz et al., 2009).

Draher and Graftmen (2002) sought to distinguish between multiple hypotheses concerning how the role the basal ganglia and cerebellum play in motor control and learning. Specifically, previous researchers have hypothesized that these regions play a role in switching attention, providing error signals regarding stimuli and rewards and/or providing an internal timing system. Using fMRI, a total of eight healthy participants engaged in an experiment involving a task-switching serial reaction task, which varied timing. The timing varied from fixed to random, and the task order varied from an unpredictable sequence to a predictable sequence, concluding with two control tasks involving set timing between stimuli and random timing between stimuli. They found the cerebellum was activated when timing became irregular, and the striatum was activated when the task order was unpredictable. Additionally, these activations were independent of whether or not the participants switched between tasks. This suggests that the cerebellum and the basal ganglia have functionally distinct roles in regards to anticipation. Specifically, the cerebellum predicts timing, while the basal ganglia predict the tasks' order.

Some researchers have theorized that symptoms of autism may be related to an impaired ability to anticipate (Allen, 2006; De Cruz et al., 2009). Allen (2006) conducted a review of articles relating to the cerebellums' impact on autism. Based on a review of studies that indicate that the cerebellum plays a fundamental role in anticipation and studies that indicate a link between the distinctions in the cerebellum and autism, Allen contended that excitatory outputs from the cerebellums of ASD individuals create unusual connectivity. This impairs the ability to anticipate, which in turn contributes to the symptoms of autism. In support of the idea that ASD persons have an impaired ability to anticipate, De Cruz et al. (2009) conducted a study comparing the performance of 52 ASD persons to 54 healthy individuals, who were matched for age, gender, and IQ, on an ocular motor task designed to provoke predictive saccades and a visually guided control task. Although there was no between-groups difference in serial reaction, the ASD participants displayed a significantly higher proportion of rightward predictive saccades. The authors concluded that these results suggest a deficit in ASD timing response.

The aforementioned studies suggest the cerebellum and basal ganglia may be involved in the ability to anticipate. Research suggests that ASD persons have unusual cerebellums and basal ganglia, and also have an impaired ability to anticipate. Muller, Pierce, Ambrose, Allen, and Courchesne (2001) found evidence suggesting that ASD individuals possess differences in reduced activation involving the cerebellum and the basal ganglia. Specifically, they used functional imaging to compare eight males with autism to eight male participants as a control on a task designed to activate the cerebellum in a controlled condition. More specifically, subjects engaged in a visually paced finger movement and a visual stimulation with no motor response. While both groups displayed significant activation within the cerebellum, the basal ganglia, and

the thalamus, ASD participants demonstrated significantly less activation compared to the control.

In addition to differences in the role involved in anticipating implicit sequences, the cerebellum seems to be involved in anticipating stimuli that are of a symbolic nature. Bo, Pelteir, Noll, and Seidler (2010) investigated the impact of the symbolic nature of stimuli on implicit learning. To conduct this study, they subjected 14 healthy participants to two experimental serial-reaction tasks, the symbolic manual and the symbolic vocal, and two control serial-reaction tasks, the spatial manual and spatial vocal. The experimental tasks differeniated from the control task in that they relied on symbolically-cued responses such as colors to indicate the appropriate response while the spatial serial-reaction task used position to indicate the appropriate response. Although Bo, Pelteir, Noll, and Seidler (2010) did not find a significant difference in reaction times between the experimental and the control group during the implicit learning sequence, they did find that participants demonstrated a lower reaction time during the symbolic sequential learning phase of the final task. Though in each task significant activation occurred in the cerebellum and the putamen during the implicit learning phases of each task, the Cerebella lobsule HVI, crus I, and crus II were only activated during the symbolic serial reaction task. Furthermore, this activation was correlated with a lower difference in activation during the final phase of the symbolic task.

In summary, this section discusses studies suggesting that unusual connectivity concerning the cerebellum and the basal ganglia may be related to an impaired ability to anticipate or predict. Specifically, this section discusses the following findings: the basal ganglia and cerebellum are associated with the ability to anticipate (Draher & Gaffman, 2002); also, that

autism is associated with an impaired ability to anticipate (Allen, 2006; De Cruz et al., 2009); and finally, that persons with autism may suffer from increased functional connectivity between the cerebellum and the basal ganglia (Muller, Pierce, Ambrose, Allen, & Courchesne, 2001).

The Purpose of this Study

Previous research indicates that persons with autism spectrum disorder have differences in the cerebellum (Allen, 2006; Courtchesne & Allen 1997, Ornitz, 1983), the basal ganglia (Qui, Adler, Crocetti, Miller, & Mostofsky, 2010; Sears et al. 1999; Weigel et al. 2010), and display reduced activation within the cerebellum and putamen (Muller, Pierce, Ambrose, Allen, & Courchesne, 2001). Further, research attests that the cerebellum and the basal ganglia are directly involved in implicit learning (Doyon et al. 1996; Pascual-Leone et al., 1993), and are linked to the ability to anticipate or predict (Draher & Graftmen, 2002). Additionally, research indicates that ASD persons suffer from an impaired performance during novel implicit learning sequences and an impaired ability to predict or anticipate (Allen, 2006; De Cruz et al., 2009). Taken together, it is logical to surmise that differences in functional connectivity in the cerebellum and the basal ganglia of autism spectrum disorder causes participants to display an impaired ability to anticipate patterns in novel sequences.

More specifically, research indicates that ASD persons have less Purkinje cells in the cerebellum (Allen, 2006; Courtchesne & Allen 1997; Ornitz, 1983). Purkinje cells are inhibitors that help modulate the dentate's excitatory outputs. Moreover, research conducted by Hoshi et al. (2004) suggests a direct bi-synaptic connection from the dentate to the putamen, which is mediated by the ventrolateral/intraluminal thalamus. Since ASD persons have less Purkinje cells compared to healthy persons, it is reasonable to anticipate a disruption in functional connectivity

between the bilateral dentate, thalamus, caudate and the bilateral putamen while engaging in a novel sequential learning task.

Through the use of archival data provided by Dr. Greg Allen, I tested a model of connectivity. The data came from 12 ASD participants and 11 participants in a control group who had undergone functional imaging while engaging in a modified serial-reaction task. The ASD participants' performances were compared on an auditory reduced motor serial-reaction task performance of healthy participants on the same tasks. Using the procedures conducted by Rissman, Gazzaley, and Desposito, (2004), I extracted fluctuations in a spatially smoothed and temporally filtered BOLD signal using the AFNI program to analyze functional connectivity. Through the use of multiple regression analysis, Sobel's Test, and univariate T-test, ASD and non-ASD functional connectivity involving the cerebellum and striatum was compared.

CHAPTER 3 METHODOLOGY

Data Source

Data came from archival records. Participants in this study include 12 adults diagnosed with high-functioning autism spectrum disorders and 11 non-ASD subjects. The individuals with ASD were recruited through a variety of sources, including local autism support groups and a local chapter of the Autism Society of America. An expert diagnostician using the Autism Diagnostic Interview-Revised and the Autism Diagnostic Observation Schedule confirmed diagnosis in the autism spectrum. Individuals were excluded from this study if they possessed a history of epilepsy, mental retardation, fragile X syndrome, or other psychiatric or neurologic diagnoses.

ASD participants were matched to the control group in terms of age (18 to 35), sex, handedness, and two subtests of the Wechsler Abbreviated Scale of Intelligence (WASI): Block Design and Matrix Reasoning. Other than these, other aspect of IQ test were not matched because, as a mental condition, autism can impact many aspects of IQ. The block design and object assembly measures are generally spared in autism.

In addition, all subjects provided written consent to participate in the original study, and all received $200.

Measures

Non-Motor Serial Reaction Task: To minimize motor activation during the implicit learning task, a modified serial-reaction task was administered. This task involves responding to a visual stimulus preceded by an auditory sequence of stimuli. The auditory stimuli consist of four tones: *A1* (500 Hz), *A2* (1000 Hz), *A3* (1500 Hz), and *A4* (2000 Hz). The visual stimuli involved the upper case letters, F, G, and R that were presented in one of two forms, either including their normal form and a mirrored form (see Figure 3). Additionally, each stimulus was presented with four general images, either upright or rotated, leaving four distinct images, upright and normal, upright and mirrored, rotated and normal, and rotated and mirrored. While each participant was exposed to these stimuli one after the other every 100 mms, they held a two-button response that corresponded to the normal or mirrored position. Also, they were instructed to use their dominant thumb for both buttons. Furthermore, they were instructed to focus attention on a central crosshair and press a button as soon as each stimulus appeared. In addition, the rotated visual stimuli were preceded by a structured auditory sequence whereas the upright stimuli were preceded by random sequences. The implicit learning sequence consisted of four tones in a seven-element sequence preceding the rotated visual stimuli, whereas the random sequence consists of four tones in a semi-random order in five, seven, or nine-elements preceding the upright stimuli. Similar to the motor serial-reaction task, the participants were exposed to the same sequence for a total of six separate trials or runs with a novel sequence introduced on the sixth run. After completion of the task, participants were asked to replicate any pattern they discovered during the task. All were unable to identify or replicate the pattern.

See Appendix E for a figure displaying the implicit learning sequence.

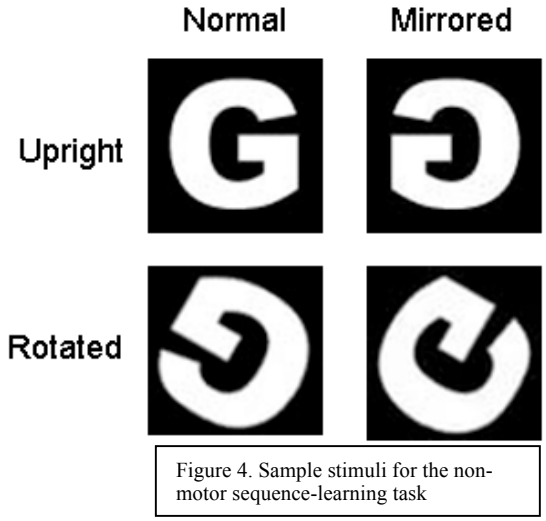


Figure 4. Sample stimuli for the non-motor sequence-learning task

Figure 3

MRI Procedures

All MRI data were acquired using a Siemens TIM Trio 3T MR system at the Meadows Diagnostic Imaging Center of the University of Texas Southwestern Medical Center. The acquisition of fMRI data was completed using time series of echo-planar images (EPI) volumes through single-shot gradient-recalled T2*-weighted EPI pulse sequence (interleaved slice acquisition; TR = 2000 ms; TE = 20 ms; flip angle = 75°; 39 3.5 mm contiguous sagittal slices; matrix = 64 x 64; FOV = 210 mm; in plane resolution = 3.3 mm x 3.3 mm). Each participant also was scanned using a three-dimensional T1 weighted image volume with contiguous 1-mm-thick slices covering the entire brain.

While being scanned with the MRI, all participants were presented visual stimuli using a

NEC LT260K DLP projector and back-projection. Audio stimuli were presented using an Avotec Silent Scan SS-100 audio system and air-conduction headphones.

Pre-Processing

All Archival FMRI data was unprocessed prior to this study. fMRI archival data were analyzed and pre processed using the AFNI software package (Cox, 1996). In order to conduct inter-subject comparisons using fMRI data, all data will be spatially normalized using the system described by Talairach and Tournoux (1998). Next, three-dimensional volume registration algorithms were applied to all imaging data as a measure to correct for each participant's movement. Following this correction, spatial smoothing and temporal filtering were applied to increase the signal-to-noise ratio. Spatial smoothing applies a Gaussian filter to remove frequencies within the BOLD signal that are likely due to physiological artifacts (Van Dijk et al., 2009). In addition to spatial smoothing, temporal filtering were employed to remove frequencies not generally associated with connectivity. Within the context of connectivity, many authors recommend removing frequencies greater than .08 Hz (Biswal , Yetkin, Haughton, & Hyde, 1995; Cordes et al. 2000; De Luca et al. 2006; Fransson and Marrelec 2008; Lowe, Mock, & Sorenson, 1998; Wu et al. 2008).

Hypotheses

Research Question 1: Will participants display functional connectivity between each dentate nucleus and contralateral putamen?

Hypothesis 1a: Connectivity between the left dentate and right putamen will predict connectivity between the right thalamus and right putamen.

Hypothesis 1b: Connectivity between the left dentate and right thalamus will predict connectivity between the right thalamus and right putamen.

Hypothesis 1c: Connectivity between the left dentate and right putamen will predict connectivity between the left dentate and right thalamus.

Hypothesis 1d: Connectivity between the left dentate and right thalamus will mediate the correlation between the left dentate/ right putamen and the right thalamus/right putamen.

Hypothesis 1e: Connectivity between the right dentate and left putamen will predict connectivity between the left thalamus and left putamen.

Hypothesis 1f: Connectivity between the right dentate and left thalamus will predict connectivity between the left thalamus and the left putamen.

Hypothesis 1g: Connectivity between the right dentate and left putamen will predict connectivity between the left dentate and left thalamus.

Hypothesis 1h: Connectivity between the right dentate and left thalamus will mediate the correlation between the right dentate/ left putamen and the left thalamus/left putamen.

Rationale 1a-h: Previous research indicates a disynaptic connection between the dentate and the putamen, which is mediated by the thalamus (Hoshi, 2004). In addition, fcMRI research contends that the cerebellum, the thalamus, and the putamen are connected (Allen et al., 2005). Furthermore, the cerebellum and the putamen are directly involved in implicit learning (Doyon et al., 1996; Pascual-Leone et al., 1993) and are linked to the ability to anticipate or predict (Draher & Grafmen, 2002). This leads to the hypothesis that functional connectivity among the dentate, thalamus, and putamen is involved in implicit learning.

Research Question 2: Do participants with autism spectrum disorder display greater functional connectivity between the bilateral dentate and the bilateral putamen compared to the control group?

Hypothesis 2a: Persons with autism spectrum disorder will display increased connectivity between the left dentate and the right putamen compared to the control group.

Hypothesis 2b: Persons with autism spectrum disorder will display increased connectivity between the left dentate and the right thalamus compared to the control group.

Hypothesis 2c: Persons with autism spectrum disorder will display increased connectivity between the right thalamus and the right putamen compared to the control group.

Hypothesis 2d: Persons with autism spectrum disorder will display increased connectivity between the right dentate and the left putamen compared to the control group.

Hypothesis 2e: Persons with autism spectrum disorder will display increased connectivity between the right dentate and the left thalamus compared to the control group.

Hypothesis 2e: Persons with autism spectrum disorder will display increased connectivity between the left thalamus and the left putamen compared to the control group.

Rationale 2a-e: Research indicates that ASD persons are demonstrating abnormalities in the putamen (Spears et al., 1999) and the cerebellum (Allen, 2006). Furthermore, these abnormalities may be due to differences in connectivity (Allen, 2006). Research has established that an anatomic excitatory connection, which stems from the cerebellum, intersects the thalamus and connects with the putamen (Hoshi, 2004). In support of this theory, Qui, et al. (2010) found that contrary to a control group, which decreased with age, the size of the putamen in ASD persons increases with age. This interaction could be due to abnormal connectivity. Specifically, a lack of Purkinje cells, characteristic of autism, could result in the strengthening of excitatory outputs through the thalamus to the putamen. This strengthening of anatomic connections could lead to an increase in the size of the putamen relative to non-autistic persons.

Research Question 3: Do participants with autism spectrum disorder demonstrate learning impairments on the implicit learning task compared to controls as indexed by reaction times?

Hypothesis 3a: Compared to the control group, participants with autism spectrum disorder will display slower learning on the implicit learning task.

Hypothesis 3b: During the implicit learning task, participants with autism spectrum disorder will display a greater increase of reaction time compared to the control.

Hypothesis 3c: During the implicit learning task, participants with autism spectrum disorder will be less likely to display a curvilinear relationship with time.

Hypothesis 3d: Persons with autism spectrum disorder will display more incorrect or missed responses on the implicit learning task.

Hypothesis 3e: Participants will display less learning during the novel sequence on run 6 compared to runs through 5 as indexed by reaction times.

Hypothesis 3f: Persons with autism spectrum disorder will display less learning on run six as indexed by reaction times

Rationale 3a-f: Research implies that persons with ASD demonstrate increased reaction times during novel sequences of the implicit learning task (De Cruz et al., 2009). Based upon this finding, ASD participants are expected to show a slower decrease in reaction time during the implicit learning task. Moreover, since a novel sequence was introduced during run 6, ASD participants are expected to show a greater increase in reaction time during the implicit learning sequence. In terms of regression, this would be represented by a significant curvilinear regression.

Analysis

The methods of analysis that I used include multiple regression analysis and MANCOVA/ATI. More specifically, I applied multiple regression analysis to test a model of functional connectivity. Further, I used MANCOVA/ ATI to compare differences in learning between participants with ASD and controls using reaction time during a serial reaction task as an index of learning. In the following section, I describe the specific applications of multiple regression analysis and MANCOVA/ ATI that I employed in my analyses. All statistical analyses were conducted with an alpha of .05.

Preliminary Analyses

As part of the preliminary analyses, each participant's reactions times were entered into SPSS and correlated with time. These coefficients were used as an index of each individual's learning at a given run. (See Appendix A for each participant's task related performance score.)

For the purpose of obtaining the random phase covariate, simple linear regression was

implemented using time as a predictor of random performance. The unstandardized regression slope was used as an index of performance on the random task. For the purpose of measuring implicit learning, curvilinear regression was employed using time as a predictor of the learning reaction times. For the purpose of this analysis, the overall regression slope was used as an index of learning over time and the slope of the curve was used as an index of the change in learning due to the change in the implicit sequence on run 6. Moreover, descriptive statistics were computed to include every participant's mean implicit learning slope and random phase reaction times during each run. Finally, data were tested for correspondence to the univariate assumptions of multiple regression analyses and the multivariate assumptions of MANCOVA/ ATI. I used the random reaction time as a covariate and implicit learning reaction time as the dependent variable while conducting the MANCOVA/ ATI.

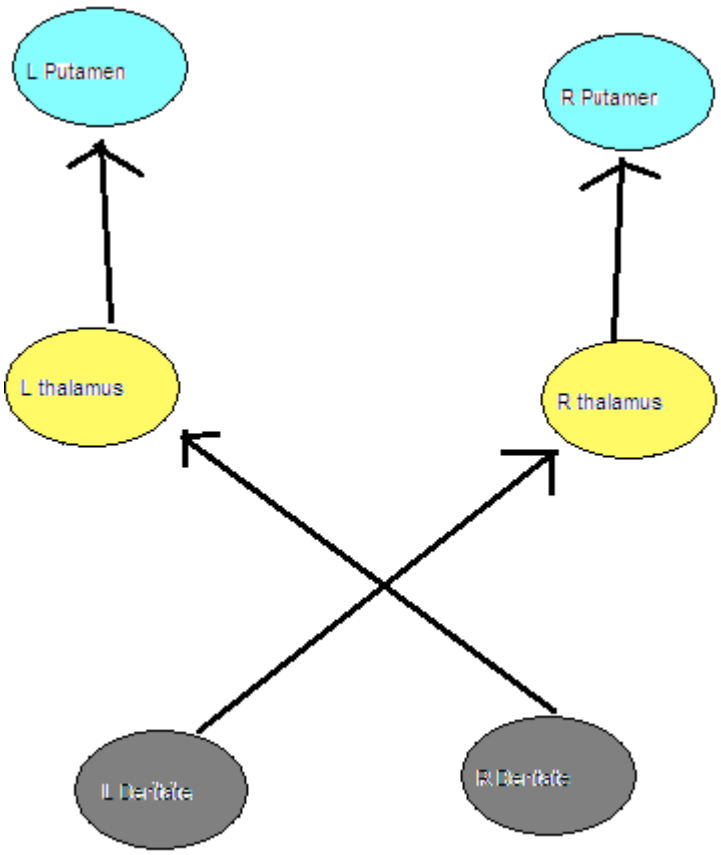


Figure 4

Isolating the signal within the dentate, thalamus, and putamen

For each participants, the dentate, putamen, and thalamus seed volumes were identified by using Talairach coordinates (Allen et al., 2005; Schmahman et. al., 2000). For the thalamus specifically, seed volumes in the ventrolateral and intralaminar, regions were identified, which are known to connect to the dentate and the putamen (Hoshi et al., 2004).

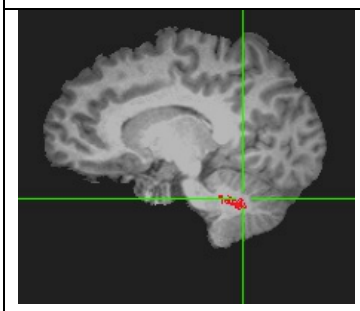
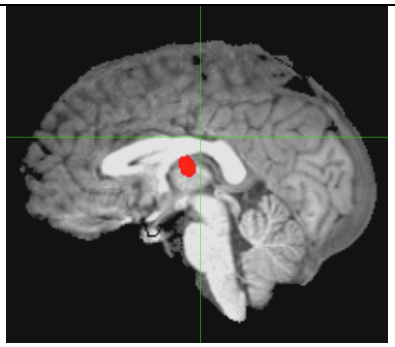
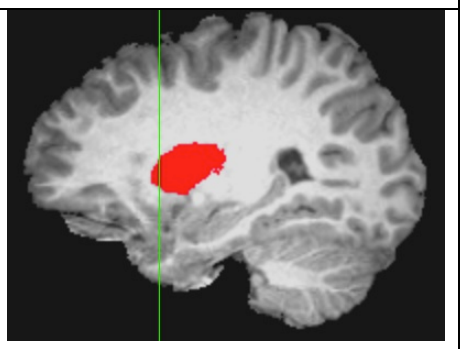
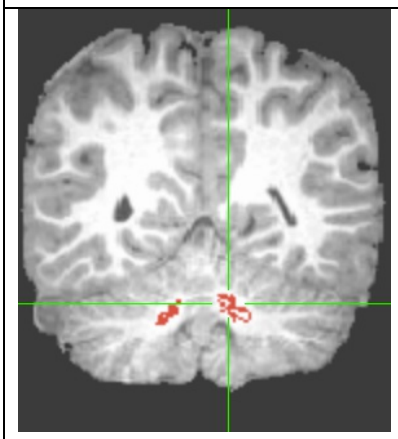
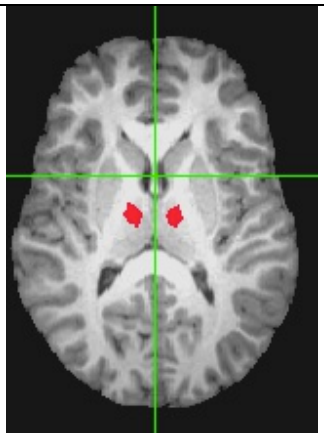
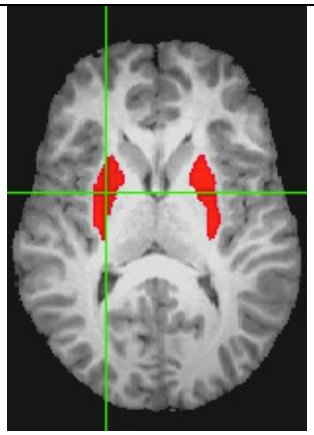
Sagittal Dentate	Sagittal Ventrolateral/ Intralaminar Thalamus	Sagittal Putamen
		
Dentate Coronal	Axial Ventrolateral/ Intralaminar Thalamus	Sagittal Putamen
		

Figure 5

Specifically, I began with a template region of interest (ROI) that could have potentially contained the specific region, overlaid this template on each individual's high-resolution anatomical data, and then edited the template to correspond to the individual's anatomy. This

was accomplished through the use of the ANFI plugin: Draw Dataset (see Figure 5). Further, anatomical atlases were used to verify the locations of the dentate, the combined ventrolateral/intralaminar thalamus, and the putamen (Allen, 2005; Courchesne et al., 1989; Press et al., 1989, 1990; Schmahmann et al., 2000; Westmoreland & Cretsinger, 2011). Finally, once each region has been identified, temporally filtered time series signal data were extracted from the voxel seed volumes. Each region's BOLD signal was extracted according to hemisphere, which was used to create two signal time courses for each region that corresponded to each brain hemisphere.

Research Question 1: Will each participant display functional connectivity between the bilateral dentate and the bilateral putamen?

Hypothesis #1 a-h: For these analyses, the ASD experimental group and the control group participants' combined run BOLD signal was extracted from each ROI described above. Multiple regression analysis was employed, using the bilateral dentate and thalamus correlation coefficient to predict the bilateral putamen hemodynamic response. If either independent variable was found to be a significant predictor of the dependent variable, then the following post hoc procedures were conducted.

First, I conducted separate simple regression analyses to analyze different patterns of connectivity between each hemisphere of the cerebellum and cerebrum. Specifically, I extracted the BOLD signal from the right dentate, thalamus, and putamen in addition to the left dentate, thalamus, and putamen. Further, I obtained functional connectivity indices by using the right dentate as the predictor of the left thalamus ($R_{Dentate->L\ Thalamus}$), the right dentate as the

predictor of the left putamen(*R Dentate->L Putamen),* the left thalamus as a predictor of the left putamen (*L Thalamus->L Putamen),* the left dentate as the predictor of the right thalamus *(L Dentate->R Thalamus),* the left dentate a predictor of the right putamen *(L Dentate->R Putamen),* and the right thalamus as a predictor of the right putamen *(R Thalamus->R Putamen)*. The unstandardized linear slopes of these coefficients were used as indices of connectivity afor each participant (see Appendix B). In order to protect against inflation of the type I error rate, Bonferroni's correction was applied to the alpha of each analysis.

Once these coefficients were obtained, simple linear regression was employed to determine if R Dentate->L Putamen was a significant positive predictor of R Dentate->L Thalamus, the R Dentate->L Putamen was a positive predictor of L Thalamus->L Putamen, and the R Dentate->L Thalamus was a positive predictor of L Thalamus->L Putamen. In parallel with the right cerebellum and left cerebrum analysis, simple regression was conducted to see if L Dentate->R Putamen was a significant positive predictor of L Dentate->R Thalamus, the L Dentate->R Putamen was a positive predictor of R Thalamus->R Putamen, and the L Dentate->R Thalamus was a positive predictor of R Thalamus->R Putamen.

If significance was found among all the variables corresponding to the right cerebellum/ left cerebrum or the left cerebellum/right cerebrum, a conditional Sobel's test for mediation (1982) was conducted to determine if either dentate-> thalamus connection mediated the relationship between its corresponding dentate-> putamen and thalamus->putamen connection. This involved a conditional ANOVA including the appropriate dentate->putamen and dentate-> thalamus to determine if these mediators are partial or full.

Research Question 2: Do participants with autism spectrum disorder display greater functional connectivity between the bilateral dentate and the bilateral putamen compared to the control group?

Hypothesis #2 a-e Analysis: For this analysis, MANOVA was employed to determine if there were group differences between the autism group and the control group among the six connectivity indices described above (i.e., R Dentate-> L Putamen, R Thalamus-> R Putamen, etc). If the overall Wilk's Lambda was significant, the between group univariate analysis was used to determine specific differences between groups among connectivity variables.

Research Question 3: Do participants with autism spectrum disorder display learning impairments on the implicit learning task compared to the control group as indexed by reaction times?

Hypothesis 3a-f: In order to compare the performance of ASD and control participants on the implicit learning task, I implemented a MANCOVA, T test, and Chi Square. In terms of a covariate, I used the unstandardized linear regression slope coefficient of the participants' performance on all the random phases. For the dependent variables, I used the unstandardized curvilinear slope coefficients as the index of implicit learning. As stated above, I included the overall regression slope as an indicator of implicit learning and the slope of the curve as the index of the change in learning due to the novel sequence introduced during run 6. If statistical

significance was found using Wilks' Lambda, I conducted individual univariate analysis to test learning specific performance differences across groups.

In order to test hypotheses 3c, Chi Square was employed. In terms of 3c, the total frequency of significant (p value < .05) curvilinear relationships with time that occur separately during the implicit learning task, and the random task, was calculated for all participants. Chi Square was implemented to compare the frequency of ASD persons, with significant relationships, to the frequency of the control, with significant relationships for the implicit learning task.

Moreover, hypothesis 3d employed an independent sample T test to compare the mean number of missed, or incorrect, items that occurred between the ASD group and the control group during the implicit learning task. This step was repeated to compare the number of missed, or incorrect, items that occurred during the control task.

In order to test hypothesis 3e and 3f, a paired sample t test and an independent sample t test were employed. Prior to conducting either t test, unstandardized linear slopes comparing individual participant reaction times to the sequential time of the *First Implicit Learning Sequence*, runs 1 to 5, and the *Second Implicit Learning Sequence*, run 6, were extracted separately. For hypothesis 3e, a one tailed paired sample t test was conducted, which compared all the participants' performances during the first sequence and the second sequence. In order to test hypothesis 3f, ASD persons' performances were compared to the control groups' performances, during the second sequence, using a one tailed independent t test.

CHAPTER 4: RESULTS

Preliminary Analysis

The Hemisphere specific BOLD signal for a total of 1,212 time points was extracted for the dentate, intralaminar thalamus, and putamen ROIs for all participants using ROI average. Individual Connectivity Coefficients for both hemispheres are displayed in Appendix B.

Table 1 the Descriptive Statistics

Variable	Autism Mean	SD	Control Mean	SD
Autism				
Right Cerebellum ->Left Hemisphere MRI				
Right Dentate-> Left Thalamus	.71	.19	-.01	.46
Right Dentate->Left Putamen	.67	.29	.15	.31
Left Thalamus->Left Putamen	.9	.09	.10	.67
Left Cerebellum-> Right Hemisphere MRI				
Left Dentate->Right Thalamus	.84	.4	.08	.26
Left Dentate->Left Putamen	.89	.40	.05	.45
Right Thalamus->Right Putamen	.91	.24	.65	1.1
Implicit Learning (n=7)				
Implicit Learning Index	-352.	218.14	-288.3	122
Learning Change	6.11	3.23	4.46	2.04
Random Sequence	-119.9	231.7	-37.67	18.78
LearningRun6	67.38	580.65	-1.8	148.65
Number of Missed Learning	7.29	6,87	2.78	2.28
Number of Missed Random	5	3.28	3.67	87

Because testing mean differences were components of analysis, Kolmogorov-Smirnova

was employed to test for violations of the normality assumption. Kolmogorov-Smirnova suggests that the assumption of normality has been violated among the control group the left dentate/ right putamen variable (.296, p<.05) and the autism group's left thalamus/left putamen (.314, p<.05).

The inspection of the L Dentate->R Putamen Variable revealed a skewness value of 2.38 with kurtosis of 8.62. A box and whiskers test revealed N9's Left Dentate->Right Putamen as a high outlier. Once N9 was removed, a new analysis revealed a skewness value of .402 and a kurtosis value of -.921. Moreover, a follow-up Kolmogorov-Smirnova test was non-significant (.144, p>.05).

The inspection of Left Thalamus->Left Putamen Variable yielded a high negative skewness value of -2.8 and kurtosis of 8.8. A box and whiskers test revealed an outlier corresponding to a2's L thalamus->L putamen. Once N9 was removed, a new analysis revealed a skewness value of .015 and a kurtosis value of -.1.270. Moreover, a follow-up Kolmogorov-Smirnova test was non-signifcant (.145 p>.05).

In addition to the assumption of normality, the box test and Levene's test were conducted for any violations of the homogeneity of covariance and the variance assumption. Homogeneity of covariance Box's Test of Equality of variance was violated (F (21, 1297.6) = 3.1.38 p<0.05). Moreover, Levene's test for equality of variance was significant on for the L Thalamus/L Putamen variable (F(1,19) = 34.91 p<.05, R Thalamus/R Putamen Variable (F(1,19) = 6.2 p<.05 and the R dentate-> L thalamus Variable (F(1,19) = 4.46 p<.05). Since the analysis of mean differences corresponding to differences in connectivity was conducted at the univariate level, there was not any post hoc test performed. Also, the f tests were robust to violations of the homogeneity of variance assumption (Lindman, 1974) and no special modifications were taken

for this analysis. Finally, since there were only two within group factors, Mauchly's Test of Sphericity was not performed.

Table 2 Describing Implicit Learning Autism-Control Differences

Variable	Mean Difference	Standard of Error	Pvalue
Implicit Learning	-73.45	89.72	.21
Learning Change	1.96	1.33	.08
Implicit run6	-180.72	148	.38

Table 3 Correlation Table Left Cerebellum/ Right hemisphere

	LDe/RPu	LDe/RTha	RTha/RPu	RDe/LPu	RDe/LThal	LTha/LPu
L Den-> R Put	1	.65**	.62**	.72**	.64**	.37
L Den-> R Thal	.65**	1	.63**	.55**	.63**	.65**
R Thal-> R Put	.62**	.63**	1	.62**	.46*	.58**
R Den-> L Put	.72**	.55**	.62**	1	.72**	.50**
R Den-> L Thal	.64**	.63**	.46*	.72**	1	.59**
L Thal->L Put	.37	.65**	.58**	.50*	.59**	1

* P< .05 one tail **p<.01 one tail

Implicit Learning Sequence

Individual Learning Sequence Index, Change in Learning Index, and the random sequence index were obtained by correlating each subject's performance with time. The Learning Sequence Index and Change in Learning Index were obtained using curvilinear regression. The overall slope was used as the Learning Index, while the slope of the curve was used as the Change in Learning Index. The random sequence control was obtained using simple linear regression. Prior to each individual's regression analysis, individual performances were inspected for outliers. Due to the overwhelming number of outliers, only outliers from the first time point were removed. These outliers were likely due to the participant adjusting to the task.

Any outlier, which the first correct response was the largest outlier, as indicated on the box and whisker test, was also removed. Subjects A1 and A9 contained outliers, which fit these criteria. Moreover, A17 didn't display any correct responses on run 6, so this participant will be excluded from any analysis related to the Second Implicit Learning Sequence, including analyses corresponding to hypothesis 3a, 3b, 3e, and 3f. In addition, A6 and N9 displayed a non-significant positive increase in reaction time over the entire sequence. Since this would indicate negative learning, participant A6 will not be included in analyses corresponding to hypothesis 3a or 3b. In terms of the mean reaction slope on run 6, the box test and whiskers test revealed N16 to be an outlier. Since regression slopes only involve nine time points, which could easily be influenced by outliers, N16 was removed for analyses corresponding to hypothesis 3e and 3f. Individual Learning Coefficients are displayed in Appendix B (Individual Learning Coefficients) and Appendix C (Implicit Learning Separated by Sequence). P-values are displayed on Appendix D (P-values for Individual Curvilinear Regression).

Since mean difference testing was employed in the analysis of learning difference, a Kologorov-Smirnov test was conducted for any normality violations for the dependent variables, learning index, and the learning curve index. Among the autism group, Kolmogorov-Smirnova did not reveal any significant violations of normality for either the Learning Curve Index (Kolmogorov-Smirnov (7)=.23 $p>.05$) or the Change in Learning Index (Kolmogorov-Smirnov (7) = .22 $p>.05$). Moreover, among the control group, a Kologorov-Smirnov test revealed similar findings for the Learning Index (Kolmogorov-Smirnov (9) = .14 $p>.05$) and the Change in Learning Index (Kolmogorov-Smirnov (9) = .15 $p>.05$).

In terms of the homogeneity of covariance and variance assumption, the Box's Test of

Equality of Variance and Levene's test were employed. The Homogeneity of Covariance Box's Test of Equality of variance was non-significant ($F(3, 9273.5) = 2.204$ $p>.05$). Likewise, the homogeneity Levine's test was non-significant for the Learning Index variable ($F(2,16) = 1.156$ $p>.05$, the Change in Learning variable ($F(2,22) = 1.467$ $p<.05$, and the run 6 learning index ($F(1,15)= .01$ $p<.05$. Additionally, certain participants' implicit learning performances were missing. Moreover, Levene's Test suggest asymmetric variance between groups for the t test comparing the number of missed or incorrect responses for the learning sequence ($F=9.74$ $p<.05$) and the Random Task ($F=4.76$ $p<.05$). Participants with missing performance scores include a8, a10, a13, and n11.

Sobel's Test for Mediation

The following section discusses the use of Sobel's test to determine if variables corresponding to connectivity between each hemisphere's dentate->thalamus mediates the relationships corresponding to each hemisphere's dentate->putamen and thalamus->putamen. Since there were expected problems relating to multi-collinearity among all the variables, simple regression will be employed with a Bonferroni correction applied to each one-tail alpha of .05. After applying a Bonferroni correction, the modified alpha corresponding to the original alpha of .05 was .008. Since Sobel's test is conditional on the correlation of the variables in the model, it was not included in determining the modified alpha. Furthermore, Table 5 illustrates unstandardized slopes, standard of errors, and adjusted r^2 corresponding to all tests discussed in this section.

Table 4: Mediation Model Correlations

Independent Variable	B	Std. Error	Adjusted r^2*

Model predicting L Dentate->R Thalamus			
L Dentate->R Putamen	.5*	.13	.39
Model predicting R Dentate->L Thalamus	.9*	.2	.49
R Dentate->L Putamen			
Model predicting R Thalamus->R Putamen			
L Dentate->R Thalamus	1.53*	.44	.36
L Dentate-> R Putamen	1.17*	.34	.36
Model predicting L Thalamus->L Putamen			
R Dentate->L Thalamus	.72*	.23	.31
R Dentate->L Putamen	.64*	.22	.27

* significant at .05 Includes Bonferroni correction

Left Dentate-> Right Thalamus as a mediator

Prior to conducting Sobel's test, multiple simple regression analyses were conducted to determine if the L Dentate->R Putamen variable was a positive predictor of R Thalamus->R Putamen variable, L Dentate->R Thalamus variable was a positive predictor of the R Thalamus->R Putamen variable, and L Dentate->R Putamen variable was a positive predictor of the L Dentate->R Thalamus variable.

Using the L Dentate->R Putamen variable as a positive predictor of R Thalamus->R Putamen variable revealed a significant relationship (B =.184 $t(21) = 2.02$, $p>.05$ $r^2 = .40$). Likewise, the analysis of the L Dentate->R Thalamus variable as a predictor of R Thalamus->R Putamen was statistically significant (B = 1.53 $t(21) = 3.5$, $p<.05$ adjust. $r^2 = .36$). Moreover, the L Dentate->R Putamen was a significant predictor of the Left Dentate->Right Thalamus (B = .184 $t(21) = 2.02$, $p>.05$ $r^2 = .40$). According to Cohen (1988), the effect sizes for all three relationships were considerably large (adjusted $r^2 > .26$). Additionally, multiple regression was

performed including L Dentate->R Thalamus and L Dentate->R Putamen as predictors of R Thalamus->R Putamen. The overall ANOVA was revealed to be significant ($F(2,20)= 10.59$ $p<.05$. Both the L Dentate/ R Putamen (B .578 $t(21)=2.88$ $p< .05$) and the L Dentate/ R Thalamus (B=.93 $t(21)=2.12$ $p<.05$) were determined to be significant predictors of R Thalamus->R Putamen.

Since a significant correlation was found among the L Dentate/ R Putamen, the L dentate/ R Thalamus, and the R thalamus/R Putamen, Sobel's test was performed using the L dentate/R thalamus as the mediator variable. As displayed by the model (L Cerebellum->R Cerebrum), Sobel's test suggests that the connectivity between the Right Dentate/Left Thalamus mediates the relationship between the Right Dentate/ Left Putamen connectivity variable and the Left Thalamus/Left Putamen variable ($z= 2.59$ $p<.05$).

a=L Dentate-> R Putamen/ L Dentate-> R Thalamus
b=L Dentate->R Thalamus/ R Thalamus-> R Putamen
Z-value = $a*b/\sqrt{(b^2*s_a^2 + a^2*s_b^2)}$
$2.59=((.5*1.53)/\sqrt{(.5^2 (.13)^2 + 1.53^2 (.44)^2)}$ $p<.05$

Right Dentate->Left Thalamus as a Mediator

Prior to conducting Sobel's test, multiple simple regression analyses were conducted to determine if the R Dentate->L Putamen variable was a positive predictor of L Thalamus->L Putamen variable, R Dentate->L Thalamus variable was a positive predictor of the L Thalamus-> L Putamen variable, and R Dentate->L Putamen variable was a positive predictor of the R Dentate->L Thalamus variable.

Similar to the results in the previous section, the R Dentate->L Putamen was a significant positive predictor of the R Dentate->L Thalamus variable (B = .90 $t(19) = 4.51$, $p<.05$ $r^2 = .50$)

and the L Thalamus->L Putamen variable (B = 1.74 t(19) = 3.44, p<.05 r^2 =. 35). In addition, the R Dentate->L Thalamus variable was a significant positive predictor of the L Thalamus->L Putamen variable (B = .1.53 t(19) = 3.5, p<.05 adjust r^2 = .36).

The overall ANOVA was revealed to be significant (F(2,20)= 5.13 p<.05. However, both the R Dentate/ L Putamen (B .505 t(21)=1.45 p< .05) and the R Dentate/ L Thalamus (B=.93 t(21)=1.32 p<.05) were determined to be non-significant predictors of L Thalamus->L Putamen. This change in significance from simple regression is probably due to a lack of statistical power since apriori power analysis for a large effect size and power of .80 requires a sample size of 31.

Since all three variables were found to have statistically significant correlations and the anatomically imposed limitations of anatomical directionality, Sobel's test was performed using the R Dentate/L Thalamus as the mediator variable. Sobel's test suggests that the R Dentate->L Thalamus mediates the relationship between the Right Dentate-> L Putamen variable and the L Thalamus->L Putamen variable (Z = 2.65 p<.05).

a= R Dentate-> L Putamen/ R Dentate-> L Thalamus
b= R Dentate->L Thalamus/ L Thalamus-> L Putamen
Z-value = $a*b/\sqrt{(b^2*s_a^2 + a^2*s_b^2)}$
$2.65= ((.9*.72)/ \sqrt{(.9)^2(.2)^2+(.72^2)(.23)^2})$ P<.05

Table 5 Comparing Connectivity for Autism-Control

Variable	Mean Difference	Std. Error	Effect Size
L Dentate->R Putamen	.84**	.19	.52
R Dentate->L Putamen	.53**	.13	.46
L Dentate->R Thalamus	.77**	.11	.73
R Dentate->L Thalamus	.72**	.15	.54
L Thalamus->L Putamen	.8**	.2	.45
R Thalamus->R Putamen	1.56**	.35	.51

* Significant at .05 ** significant at .01. Includes Bonferroni correction.

Differences in Connectivity

Multivariate analysis was employed to test mean connectivity differences among the autism group and the control. The multivariate testing differences in connectivity between autism and the control using Wilks' Lambda was statistically significant ($f(6, 14) = 12.25$ $p<.05$). See Table 6 (autism/control connectivity differences).

For connectivity indexes measuring the right cerebellum/left hemisphere, the univariate analysis suggests significant differences between groups among the Right Dentate->Left Putamen connectivity variable ($f(1,19) = 16.458$ $p<.05$ $\eta^2 = .46$), Right Dentate->Left Thalamus connectivity variable ($f(1,19) = 22.140$ $p<.05$ $\eta^2 = .54$), and Left Thalamus/->Left Putamen connectivity variable ($f(1,19) = 15.60$ $p<.05$ $\eta^2 = .45$). Moreover, Partial Eta Square reveals large effect sizes for each variable ($\eta^2>.15$)

For connectivity indices measuring the left cerebellum/right hemisphere, the univariate analysis suggests significant differences between groups among the Left Dentate->Right Putamen connectivity variable ($F(1,19) = 20.67$ $p>.05$ $\eta^2 = .52$), the Left Dentate -> Right Thalamus connectivity variable ($f(1,19) = 50.56$ $p<.05$ $\eta^2 = .73$), and Right Thalamus->Right Putamen connectivity variable ($f(1,19) = 20.665$ $p<.05$ $\eta^2 = .51$). Furthermore, Partial Eta Square reveals large effect sizes for each variable ($\eta^2>.15$).

Table 6 Paired Sample T test Sequence One to Sequence Two

Variable	Mean Difference	Standard of Error	Pvalue
Run 1 to 5 –Run 6	-339.41	148.7	.018*

* P< .05 one tail **p<.01 one tail

Implicit Learning Differences

A MANCOVA was employed to contrast group performance between the autism group and the control group on the Learning Index and the Change in Learning due to a novel sequence while controlling for performance on the random task. The overall multivariate Wilk's Lambda was non-significant ($f(2,12) = 1.67$ $p>.05$). Since apriori power analysis with a medium effect size and a power of .8 would require a sample size of 68, there is a strong possibility that this lack of significance was due to a lack of power. Due to a possible lack of power, an exploratory pairwise comparison will be conducted. Between subjects analysis of the effect of autism on the Learning Index was non significant ($f(1,15) = .67$ $p = .22>.05$ $\eta 2 = .09$). Change in Learning Index was just short of significant with a notable effect size ($f(1.15) = 2.16$ $p = .08>p.05$ $\eta 2 = .13$).

Table 7 Chi Square test Comparing Task comparison

Variable	Count	Expected	Total	Chi Square
Learning Task				4.34*
Autism	2	4.3	8	
Control	7	4.7	9	
Control Task				.038
Autism	5	5.2	8	
Control	6	5.8	10	

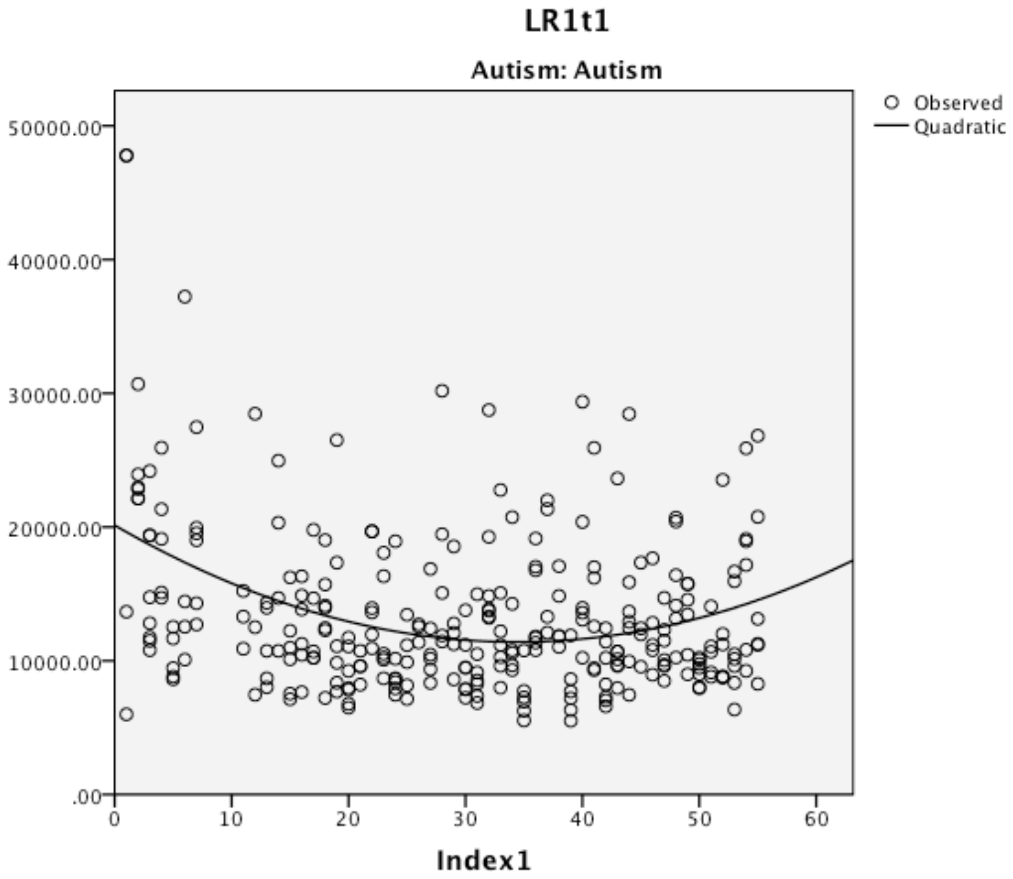
This table compares the number of participants whose curvilinear regression models revealed p values<. 05.

Separate Chi Square test were conducted to compare the ASD group and the control group on the frequencies of significant curvilinear regression coefficients involving performance improvements with time during the implicit learning task, the number of missed or incorrect answers during the implicit learning sequence, and the number of missed or incorrect answers

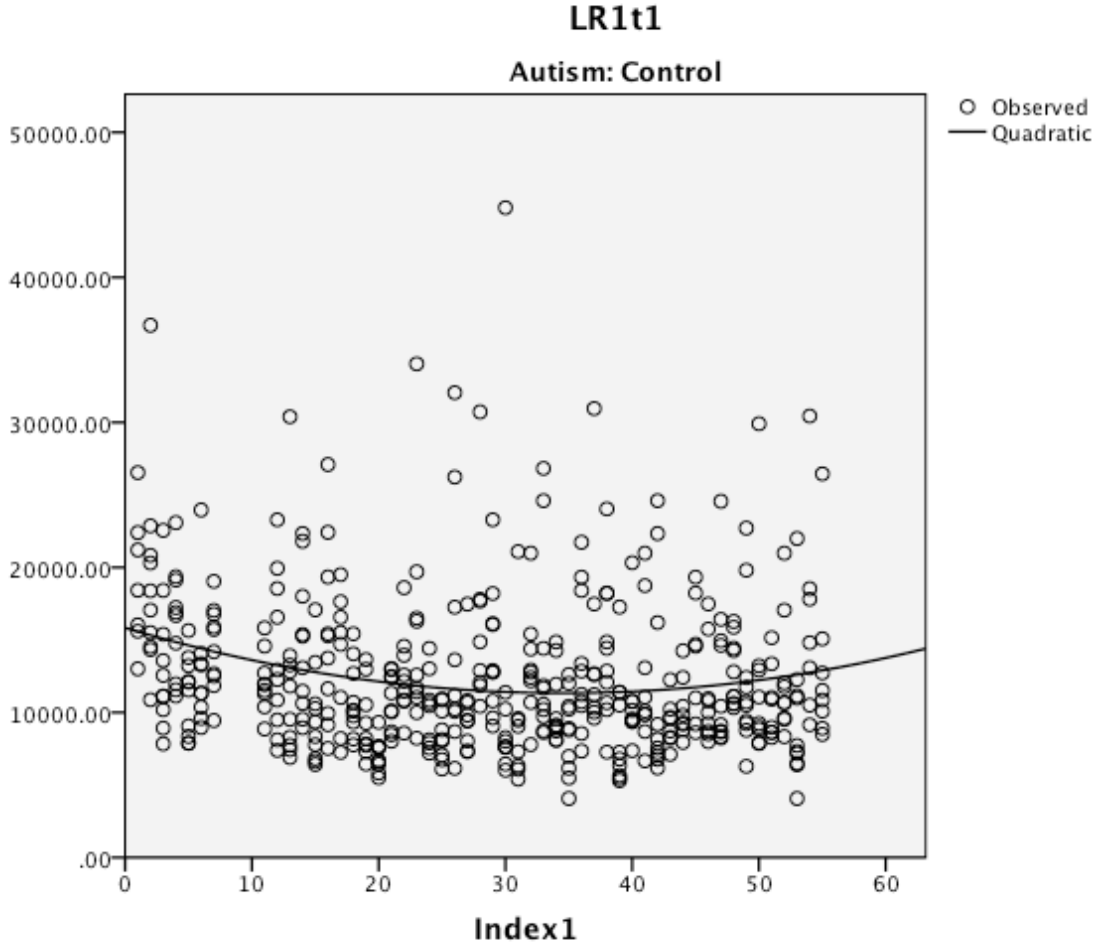
during the random sequence. The Chi Square tests reveal that less ASD participants demonstrated significantly more curvilinear relationships overtime (X^2 (1, N=19) = 4.37 p<. 05 Cramer's V=.48).

In terms of missed or incorrect answers, the T test revealed that ASD group missed significantly equivalent number of items on the learning task (T (7.03) = 1.66 p> .05 and the random task (T (6.05) = .924 p<. 05.

Finally, T tests were conducted to compare the learning indices for sequence one to sequence two and ASD participant performance on the second sequence to the control group. Paired samples T test indicate an decrease on performance during sequence two compared to sequence one (t(16)=-2.38 p<.05). However, ASD persons did not display any significant decrease in performance on run 6 (t(15)=.56 p>.05). Based of an apriori power analysis, this is likely due to a lack of power. Specifically, Gpower determines that a medium effect size and power of .8 would require a sample size of 51 per sample.



This Graph represents the curvilinear relationship between ASD participants performance on the Implicit Learning Task and Time. Number 47 on the x axis is when Sequence Two was introduced.



This Graph represents the curvilinear relationship between the control groups Performance on the Implicit Learning Task and Time. Number 47 on the x axis is when Sequence Two was introduced.

CHAPTER FIVE: DISCUSSION

The aim of this study was to investigate the impact of autism spectrum disorder on functional connectivity between the cerebellum and the basal ganglia in addition to implicit learning. More specifically this study sought to test a model of connectivity to: (a) determine if functional connectivity between the dentate and the thalamus mediates functional connectivity between the dentate and the putamen; (b) determine if autism spectrum disorder participants display higher levels of functional connectivity compared to a control group; and (c) compare the performance of ASD participants to a control group on an implicit learning task.

Research Question 1: Will participants display functional connectivity between the bilateral dentate and the bilateral putamen?

The hypothesis relating to participants displaying functional connectivity between the bilateral dentate and bilateral putamen was supported by these findings. Specifically, evidence suggests that functional connectivity between the Right Dentate/ Left Thalamus positively predicts connectivity between Left Thalamus/Left Putamen. This was also evident when examining functional connectivity between the Left Dentate/Right Thalamus. Since the BOLD signals related to whole brain, cerebrospinal fluid, and white matter was were removed from the analysis, this analysis suggests a correlation among grey matter BOLD signal between the bilateral dentate/thalamus and the bilateral thalamus/putamen. This indicates that the correlation of the signal coming from the neural cell bodies within the dentate and the thalamus predicts the correlation of the signal from the neural cell bodies within the thalamus and the putamen. Since

evidence indicates an excitatory anatomical connection stemming from the dentate through the thalamus and then the putamen, these functional connections would be correlated with the known anatomy.

Further support for this hypothesis is the fact that connectivity between dentate/ putamen positively predicted the connectivity among between dentate/ thalamus and thalamus/ putamen. Taken together with previous findings, this indicates a strong relationship between the connections of all three structures on both hemispheres. Together with Hoshi's findings, this indicates that the ventrolateral/intralaminar thalamus mediates the connections between the dentate and the thalamus. Based conditionally on the significance of these correlations and evidence of anatomical directionality, a Sobel's test provided further evidence for mediation for the dentate and putamen by the right dentate/left thalamus variable and the left dentate/right thalamus respectively.

One interesting finding was that the L Dentate->R Thalamus was only a partial mediator to the relationship with L Dentate->R Putamen and R Thalamus-> R Putamen. This suggests that other factors contribute to the relationship between the L Dentate->R Putamen and R Thalamus-> R Putamen. One possible explanation for this is that another anatomical path, such as the one indicated by Bostan, Dum, and Strick (2010), could connect the putamen and the dentate. This would bypass the thalamus and explain the partial mediation seen in these findings.

Due to the low power in this study, these results were unable to establish whether the R Dentate->L Thalamus mediation was partial or full. Rather, this interpretation relies heavily on the findings of previously established anatomical connections among the three structures. Specifically, the dentate is a known output region of the cerebellum, which sends excitatory

connections to the ventrolateral/intralaminar thalamus. Moreover, Hoshi e al. (2004) has established that connections continue on the putamen of the basal ganglia. While it is possible that another pathway could connect the basal ganglia to the dentate, as indicated by Bostan, Dum, and Strick, evidence suggests involvement of the R Dentate->L Thalamus pathway. Specifically, the only connecting point involving the dentate, ventrolateral/intralaminar thalamus, and the putamen is the one indicated by Hoshi et al (2004). It is possible that undiscovered connections may allow for partial mediation or may challenge the role of the thalamus as the mediator. Based upon the role of the structures, and the research findings by Hoshi et al. (2004), it is likely that the thalamus partially mediates the relationship between the dentate and putamen.

Research Question 2: Do participants with autism spectrum disorder display greater functional connectivity between the bilateral dentate and the bilateral putamen compared to the control group?

Results would support this hypothesis. More specifically, this hypothesis states that ASD persons have greater connectivity among the three structures discussed. These findings indicate that connectivity among the bilateral dentate/putamen (R Dentate/ L Putamen and L Dentate/R Putamen), dentate/thalamus (R dentate/L thalamus and L Dentate/R Thalamus), and thalamus/putamen (L Thalamus/L Putamen and R Thalamus/R Putamen) was greater among ASD participants compared to the control group.

When considering Hoshi et al. (2004) and the results from testing the mediation model, these findings would help to interpret previous findings in the literature that discuss anatomical differences in the cerebellum (Allen, 2006; Courchesne and Allen 1997, Ornitz, 1983) and the

basal ganglia (Qui, Adler, Crocetti, Miller, and Mostofsky, 2010; Sears et al., 1999; Weigel et al., 2010). As discussed by Allen (2006), the lack of Purkinje cells in the cerebellum may lead to increased excitatory connections stemming from the dentate to the putamen, which could explain the greater connectivity demonstrated in these results. This increase in connectivity could lead to the striatal differences observed by Qui, Adler, Crocetti, Miller, and Mostofsky (2010) or the increase in the size of the putamen observed by Spears et al. (1999). Specifically, if ASD persons possess greater connectivity, it might lead to an inflated signal stemming from the dentate to the putamen. This inflated signal could lead to increases in neural connections within the putamen, which would account for the size differences.

This increase in neural connections might also be why effect size for the left dentate and the right thalamus appeared larger than the other effect sizes ($\eta^2 = .73$). For instance, Hollander et al. (2005) found a significantly larger right caudate among ASD persons compared to a control group, and Langen, Durston, Staal, Pamen, and Engeland (2007) found that the size of the caudate increased over time in contrast to the size of the caudate of the control group. The larger effect size may be due to this increase in connectivity from the right dentate and left thalamus increasing excitatory connections to the striatum. This would explain the increase in caudate size.

Finally while this study has not directly linked increases in connectivity to decreases in activation, another possible side effect of abnormal increases in connectivity among ASD persons could result in the reduced activation displayed among autism spectrum disorder participants' cerebellum and putamen (Muller, Pierce, Ambrose, Allen, & Courchesne, 2001). This speculation would be based on the idea that increased connections might increase the

baseline signal to a degree that the impact a potential hemodynamic response would be diminished. In support of this idea, Kennedy, Redclay, and Courchesne (2006) found that ASD participants 'failed to deactivate' in several regions of the brain. While the cerebellum, thalamus, and the putamen were not the regions examined in this study, it is possible that similar problems are present in the regions implicated in this study.

Research Question 3: Do participants with autism spectrum disorder display learning impairments on the implicit learning task compared to the control as indexed by reaction times?

In terms of this hypothesis, findings are mixed. Specifically, hypotheses 3a, 3b, 3d, and 3f were not supported, but 3c and 3e were supported. This would indicate that less ASD persons displayed significant curvilinear improvement on the task (hypothesis 3c) and displayed more incorrect responses on the learning task (hypothesis 3d). Moreover, hypothesis 3e indicates that both groups, of participants, demonstrated less learning upon introduction of the second sequence, which suggests that the curvilinear response is indicative of the novel sequence introduced on run 6. However, the ASD participants did not demonstrate any impairments when comparing the learning indices and controlling for performance on the random task (hypothesis 3a). The change in learning index p value fell just above the indicated alpha, signifying that ASD participants were not impaired during the transition to the second sequence (hypothesis 3b). Finally, evidence indicates that neither group out performed the other during run 6 (hypothesis 3f).

This paradox could lead to two conclusions. One possible conclusion is that the ASD

persons, who displayed improvement, demonstrated enough improvement to compensate for those who did not. If this were true, it would be in contrast to previous research demonstrating that ASD persons have an impaired ability to learn and predict implicit sequences (De Cruz et al., 2009. The final possibility involves the lack of power for the MANCOVA (n 68= power. 8) or the T test (n 102= power. 8). To support conclusion, the chi-square analysis for hypothesis 3c revealed that less participants in the ASD group displayed significant curve linear learning. While this suggests strong evidence for learning, it is based on the assumption that the significant curvilinear relationships were not linear. When regression coefficients were extracted, it was assumed that the introduction of a new sequence would provoke a curvilinear relationship. It was beyond the scope of this study to assess whether each participant's performance was actually curvilinear instead of linear. Rather, hypothesis 3e provided evidence for a curvilinear relationship. Additionally, considering that only two ASD participants displayed significant relationships, compared to seven amongst the control, any regression coefficient used, as an index of learning, could be called into question on the basis that it is not significantly different. In conclusion, the most parsimonious deduction would be that ASD participants demonstrated a difference in learning, but there is not adequate power to determine if this difference was due to impairments in implicit learning.

Limitations

It is important to acknowledge certain limitations to the current study. The first relates to correlational analysis. Specifically, functional connectivity MRI is based on correlational analysis. While this analysis revealed evidence of a relationship among BOLD signal

fluctuations, it does not establish causation or direction. Rather it contends that while correlated, the role of the thalamus as a mediator is likely due and conditional upon the anatomic connections established by Hoshi et al. (2004). Other possible pathways may exist.

One possible alternative relates to the nature of correlational research. Specifically, it is possible that these connections may be nested within other unknown variables. As stated by Ramachandran (1994), "The brain contains 100 billion nerve cells, each of which makes 1,000 to 10,000 contacts with other nerve cells. The number of possible 'brain states', or permutations and combinations of connections, exceeds the number of elementary particles in the universe." With such a large number of connections, there may be a gargantuan number of possible connections yet to be discovered. With this in mind, there may be other routes of connectivity that could explain the results of this study. Based on our current knowledge, however, the only known anatomical connections among these regions support these findings.

Another limitation is that this study doesn't address a direct link between the fcMRI data and the behavioral data. During the preprocessing of this study, the signals relating to MRI activation were removed. In other words, the findings do not reflect directly on the task. Rather, they consider solely the connections between regions, independent of any hemodynamic change relating, to the task.

Future Directions

Based on these findings, it is important to suggest possible future research directions. For example, this study was unable to determine if there are implicit learning impairments among ASD participants. However, this study did conclude that there were impairments in learning, and these impairments could be due to an impaired ability to anticipate implicit sequences.

Considering the non-significant findings suffered from weak power, and the participants were sampled from high functioning ASD participants, there is a significant possibility of type II error. Specifically, the impairments in anticipating implicit sequences could be more exaggerated among low function ASD persons. Future studies could conduct a similar analysis but with a larger sample size, or analyses that are more powerful, such as Bayesian methods which can. Since this found that learning was normally distributed, the inclusion of a normal prior distribution would increase the power of the sample.

Another possible direction for this study could cross validate the meditational model for each group separately. As previously discussed, this study found evidence for mediation when groups were pooled. The mediation models may vary across groups. When considering the how both groups varied in connectivity from one another, a future study could determine whether this model varies across groups. Future studies could cross-validate this meditational model to each group separately.

Another interesting possibility would involve combining fMRI, fcMRI, and the serial reaction task. Methods, such as those used by Rissman, Gazzaley, and Desposito (2004), could use fMRI activation coefficients to link functional connections, in these regions, to implicit learning more directly. This would aid in determining how much of a role, if any, functional connectivity plays in implicit learning. Moreover, combining this analysis with methods presented by Kennedy, Redclay, and Courchesne (2006) to see if "failing to deactivate" (p. 8275), found in other regions of the ASD brain, is also found in cerebellum, thalamus, and striatum.

Another possible direction involves determining if functional connectivity exists among

the three regions used, in this study, and the right caudate. Many previous studies found abnormalities in the caudate, especially on the right hemisphere (Hollander et al., 2005; Langen, Durston, Staal, Pamen, & Engeland, 2007; Spears et al. 1999). This study found evidence that the impact of ASD on the L dentate->R thalamus was the strongest. A future study could employ Rissman, Gazzaley, and Desposito (2004) methods to investigate whether the functional connections involving the dentate and thalamus impact, or predict, activation in the right caudate.

While ASD may be related to increased connectivity, this study does not look at the impact of this connectivity to classic symptoms of autism spectrum disorder. One potential area of interest relates to empathy. ASD persons tend to suffer from irregularities in terms of making eye contact and eye saccades (Hikosaka, O; Takikawa, Y; Kawagoe, 2000). Considering eye contact is critical to developing empathy, and the fusa facial form is connected to the basal ganglia, future studies could see if functional connectivity extends from the dentate to the fusa facial area.

Appendix (or Appendices)

Appendix A: Individual Learning Performance

Participants	Learning Index	Change in Learning	Random Control
A1	-169.24	2.6	-616.09
a2	-161.456	2.802	-17.61
a4	-330.578	7.499	-7.88
a5	-721.226	9.208	-58.87
a6	192.718*	-4.133*	-88.74*
a9	-567.06	11.04	-94.84
a14	-171.24	4.696	170.89
a15	-343	4.918	-86.13
a17	-259.644*	2.55*	-248.68*
n5	-231.897	2.988	-151.32
n6	-115.498	1.165	-56.49
n7	-374.58	4.82	-55.73
n8	-417.209	6.365	-56.62
n9	9.506*	-0.299*	-1.38*
n10	-320.27	5.424	67.07
n12	-111.637	1.917	-55.89
n15	-313.972	6.001	22.11
n16	-455.32	7.043	-71.76
n17	-254.268	4.376	-16.73

*Removed from Analysis

Appendix B: Individual Connectivity Correlations

Participant	R Dentate/ L Putamen	R Dentate/ L Thalamus	L Thalamus/ L Putamen	L Dentate/ R Putamen	L Dentate/ R Thalamus	R Thalamus/ R Putamen
n7	.69	-.10	-.45	.40	-.27	.19
n8	.43	.34	.79	-.43	.29	-.43
n9	.55	-.02	.80	4.34	.56	2.26
n10	.27	.42	.69	.57	-.03	-.04
n11	-.12	-.29	.74	-.11	.06	-.06
n12	.29	.36	.77	.18	.13	.49
n15	-.12	.04	-.87	.84	-.02	-1.58
n16	-.22	-1.11	.12	-.15	.59	-.28
n17	-.16	.21	-.77	-.40	.27	-.51
n5	.43	-.24	-.38	.15	-.27	-.83
n6	-.05	.31	.39	-.51	.10	-3.47
a1	.91	.67	.85	1.19	.72	.79
a4	.57	.59	1.05	.81	.88	.98
a2	-.13	.63	-.02	.47	.02	.69
a5	.77	.80	.98	.99	.85	1.06
a6	.75	.86	1.03	1.35	1.25	1.09
a8	.46	.58	.96	.43	.61	1.00
a9	.37	.38	.91	.01	.39	.73
a10	.87	.88	.95	.97	.92	.98
a12	.80	.73	.80	1.26	.86	.82
a13	.58	.70	.75	.82	.92	.29
a14	1.20	1.07	.84	1.23	1.13	1.08
a15	.17	.54	.81	.80	.82	1.17

Appendix C: Implicit Learning separated by Sequences

	Implicit Learning run1to5	Implicit Learning run 6
A1	-284.14	493.13
a2	-164.99	-186.73
a4	-117.43	-390.27
a5	-784.06	-125.42
a6	-62.96	-640.22
a9	-844.04	986.60
a14	-180.26	694.07
a15	-297.17	-292.09
a17	-92.40	0
n5	-300.09	109.83
n6	-92.25	-397.23
n7	-480.72	-231.95
n8	-519.78	-91.25
n9	-140.33	-491.98
n10	-213.07	721.99
n12	-85.45	-245.80
n15	-296.51	502.75
n16	-261.09	1757.32*
n17	-384.03	107.30

*Removed outlier

Appendix D: P-values for Individual Curvilinear Regression

	P values for Curvelinear Learning	Pvalue Curvelinear Random
A1	0.23	.010*
a2	0.26	.15
a4	0.15	.13
a5	.00*	.000*
a6	0.43	.26
a9	0.005*	.000*
a14	0.19	.000*
a15	0.13	.12
a17	0.09	.006*
n5	0.014*	.000*
n6	0.034*	.002*
n7	.000*	.000*
n8	0.010*	.27
n9	0.49	.08
n10	0.26	.12
n12	0.23	.000*
n15	0.03*	0.12
n16	0.004*	.000*
n17	0.00*	.036*

* sig P<.05

Appendix E: The implicit Learning Sequence

Study Begins

Auditory stimuli are 500 (A_1), 1000 (A_2), 1500 (A_3), and 2000 Hz (A_4) binaural tones

Visual Stimuli are the upper case letters G, F, and R presented in the center of the screen.

Run 1: Novel Learning sequence includes the following audio tone sequences a, d, b c, a, b, c

Stimuli are presented in the following order:

1. Learning	11. Random
2. Random	12. Random
3. Random	13. Learning
4. Random	14. Learning
5. Random	15. Learning
6. Learning	16. Learning
7. Random	17. Learning
8. Learning	
9. Learning	
10. Learning	

Run 2:

Learning Sequence: a, d, b c, a, b, c

1. Random	11. Learning
2. Random	12. Learning
3. Random	13. Learning
4. Learning	14. Learning
5. Random	15. Random
6. Learning	16. Random
7. Learning	17. Learning
8. Random	18. Random
9. Random	19. Learning
10. Learning	

Run 3

Learning Sequence: a, d, b c, a, b, c

1. Random 2. Learning 3. Random 4. Learning 5. Random 6. Random 7. Random 8. Random 9. Random 10. Random 11. Random	12. Learning 13. Learning 14. Random 15. Learning 16. Learning 17. Learning 18. Learning 19. Learning
Run 4 *Learning Sequence:* a, d, b c, a, b, c	
1. Learning 2. Learning 3. Random 4. Learning 5. Random 6. Random 7. Learning 8. Random 9. Learning 10. Random	11. Random 12. Learning 13. Learning 14. Random 15. Random 16. Random 17. Learning 18. Learning
Run 5: *Learning Sequence:* a, d, b c, a, b, c	
1. Random 2. Random 3. Random 4. Learning 5. Random 6. Random 7. Learning 8. Learning 9. Learning 10. Learning	11. Random 12. Random 13. Learning 14. Random 15. Learning 16. Learning 17. Random 18. Learning
Run 6 *Novel Learning Sequence*: c, a, b, c, d, b, a	

1. Random 2. Learning 3. Random 4. Learning 5. Learning 6. Random 7. Learning 8. Learning 9. Learning 10. Random	11. Random 12. Learning 13. Random 14. Random 15. Random 16. Random 17. Learning 18. Learning
END OF TASK	

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